A STUDY OF THE CLINICAL PROFILE OF SEVERE SEPSIS IN CHILDREN AND THE ASSOCIATION, IF ANY, OF URINARY LIVER- TYPE FATTY ACID BINDING PROTEIN(L-FABP) WITH MORTALITY, MORBIDITY AND DIAGNOSIS OF ACUTE KIDNEY INJURY

A dissertation submitted to the Tamil Nadu

Dr.MGR Medical University, Chennai for

MD Degree in Pediatrics

May 2018

CERTIFICATE

This is to certify that the dissertation titled **" STUDY OF CLINICAL PROFILE OF SEVERE SEPSIS IN CHILDREN AND THE ASSOCIATION, IF ANY, OF URINARY LIVER-FATTY ACID BINDING PROTIEN(L-FABP) WITH MORTALITY, MORBIDITY AND DIAGNOSIS OF ACUTE KIDNEY INJURY"** is the bonafide work done by Dr. Merlyn Nisha J. in the Department of Paediatrics, Christian Medical College and Hospital, Vellore towards partial fulfillment of the degree of MD Paediatrics for the examination of the The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamilnadu, to be held in May 2018.

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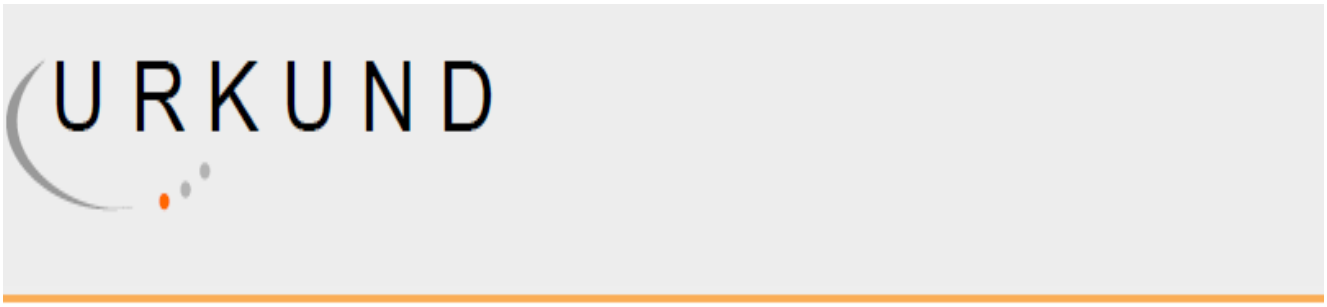

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Abstract:

Title: A study of clinical profile of severe sepsis in children and the association, if any, of urinary Liver Type Fatty Acid(L-FABP) with mortality, morbidity and diagnosis of acute kidney injury.

Department: Department of Pediatrics, Christian Medical College, Vellore.

Name of the candidate: Dr. Merlyn Nisha. J

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Background: Severe sepsis has a worldwide incidence of 8.2% and is the most common cause of admission to Pediatric ICU. Sepsis-associated AKI is the leading cause of mortality amongst children. Many biomarkers have been tried for early diagnosis of AKI; one such is L-FABP reported to be useful in predicting AKI, mortality and multi-organ dysfunction in children with severe sepsis.

Objectives: (1) To study the clinical profile of severe sepsis and identify risk factors associated with poor outcome (2) To measure the levels of urinary L-FABP in children with severe sepsis (3) To assess the association of LFABP in the diagnosis of AKI (4) To assess the correlation between urinary L-FABP levels and PELOD score in predicting mortality (5) To compare the levels of urinary L-FABP in survivors and non-survivors of severe sepsis.

Design: Prospective- observational study

Materials and methods: The study was conducted between January 2017 and August 2017 in PICU. A total of 47 children with severe sepsis were enrolled .Their clinical course and outcome was recorded. Serum Creatinine was done at admission and on a daily basis thereafter. Urine specimen was collected for L-FABP assay within 4 hours of admission and once at 48 hours and stored at -20°c till analysis by a commercial ELISA kit (Hycult Biotech, USA- Cat # HK 404-01). The obtained data was analysed using appropriate statistical tools.

Results

A total of 47 children were admitted with severe sepsis. The incidence of severe sepsis was 7.5 % (47/650). Fever was the commonest symptom present in 76.5%. Primary sepsis was present in 40/47(85%) and secondary sepsis in 14.8%. Blood culture was positive in 13/47(27.6%). The commonest organism was Pseudomonas. Acute Kidney Injury was present in 53.1% (25/47). Only oliguria was found to be a significant risk factor for AKI ($p = 0.043$). The mortality in children with Sepsis-associated AKI (SA-AKI) was 66.7% (16/24), while the overall mortality was 51.1%(24/47). The median value of L-FABP in children with AKI was 39.42(7.64-190.35) at baseline and at 48 hours was 24.05(4.5-114.05). L-FABP levels at admission were significantly elevated in non-survivors of severe sepsis compared to survivors ($p=0.048$). PELOD score had a significant correlation with mortality ($p<0.001$).

Conclusion: Acute Kidney injury remains a significant cause of morbidity in children with severe sepsis and mortality remains high. L-FABP estimation levels at admission are predictive of non-survival in children with severe sepsis. It is also a predictor of MODS. PELOD was confirmed to be a good score to assess mulit-organ dysfunction and AKI.

Key words: severe sepsis, acute kidney injury, liver-type fatty acid binding protein

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INTRODUCTION

Severe sepsis with a reported global prevalence of 8.2% is one of the most common cause of admissions to Paediatric Intensive care unit(ICU)(1). The mortality continues to be high with development of multi-organ dysfunction and acute kidney injury(AKI) being major among them. Early diagnosis of AKI may significantly improve the outcome and decrease mortality. Diagnosis of acute kidney injury, by definition is dependent on serum creatinine. Serum creatinine is marker of renal function and not injury. With homeostatic mechanisms in play the rise in serum creatinine levels does not happen until substantial renal injury has happened Hence an early marker of renal injury is preferred. Several promising biomarkers have already been reported in literature and many more are under way.

In recent times, biomarkers are being evaluated as early indicators of AKI, some of which appear more promising than others. Liver-type Fatty acid binding protein (L-FABP) is one such promising biomarker for early detection of AKI. Literature , though limited shows L-FABP to be a promising biomarker which is not only as an early indicator of renal injury but also for predicting mortality in patients with severe sepsis.

The outcome of this study will document the clinical profile of children with severe sepsis and identify factors associated with poor outcome/mortality in the Indian context. In addition the association of L-FABP as a predictor of mortality and early indicator of renal dysfunction in sepsis will be known. Since multiple

organ dysfunction (MODS) is in itself a predictor of mortality and is associated with poor outcome, having a scoring system to measure the risk of MODS helps in improving the outcome. In our study we propose to use the Paediatric logistic organ dysfunction score (PELOD) to predict the risk of organ failure and mortality. Also, the correlation of PELOD scores with L-FABP levels, if any, will indicate the utility of this biomarker if not as a replacement but as an additional tool for detecting organ dysfunction in children with severe sepsis.

AIMS AND OBJECTIVES

Aims:

This study aims to compile the clinical profile of severe sepsis in children to identify factors associated with poor outcome. The association, if any, of a urinary biomarker (L-FABP) with poor outcome/mortality as well as diagnosis of AKI will also be assessed.

Objectives :

Primary outcome :

1. To study the clinical profile of severe sepsis and identify factors associated with poor outcome (mortality and morbidity) in children
2. To measure the urinary levels of Liver-type fatty acid binding protein(L-FABP) in children with severe sepsis
3. To assess the association, if any, between L-FABP and diagnosis of acute kidney injury in the study population

Secondary outcome:

1. To assess the correlation between urinary L-FABP levels and PELOD score (Paediatric logistic organ dysfunction score)
2. To compare the levels of urinary L-FABP in children with severe sepsis amongst survivors and non-survivors

LITERATURE REVIEW:

Sepsis is the most common cause of death in infants and children worldwide. The global prevalence of severe sepsis is 8.2% and it is one of the most common causes of admission to Pediatric Intensive care unit (1). Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). It is one of the most serious and potentially life-threatening infectious diseases in childhood.

SEVERE SEPSIS IN CHILDREN:

Sepsis is a clinical syndrome resulting from a dysregulated systemic inflammatory response to infection (1). It is characterized by a generalized pro-inflammatory cascade, which may lead to widespread tissue injury. It encompasses a clinical spectrum of severity, including severe sepsis, septic shock and multi-organ failure (2). Sepsis is a leading cause of morbidity and mortality worldwide. The largest epidemiological reports of the incidence of severe sepsis in children come from US cohort studies which was done by Watson RS et al and Hartman ME et al, published in the year 2003 and 2013 respectively(5). These studies show a rising annual incidence of severe sepsis over this period of time (0.56 to 0.89/1000 children) across all age groups. The incidence of severe sepsis in these cohorts was significantly higher in younger age groups (incidence in the neonatal age group and infants aged <1 year was 9.7 and 2.25 cases per 1000 children respectively)(5).

International consensus definitions for Pediatric sepsis defines sepsis is as shown below:

TABLE 1.INTERNATIONAL CONSENSUS DEFINITION FOR PEDIATRIC SEPSIS

Infection	Suspected or proven infection or a clinical syndrome associated with high probability of infection
SIRS	Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count: 1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter) 2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli or Unexplained persistent elevation over 0.5-4 hr or In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease) 3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia 4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils
Sepsis	SIRS plus a suspected or proven infection
Severe sepsis	Sepsis plus 1 of the following: 1. Cardiovascular organ dysfunction, defined as: • Despite >40 mL/kg of isotonic intravenous fluid in 1 hr: • Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age or • Need for vasoactive drug to maintain blood pressure or • 2 of the following: • Unexplained metabolic acidosis: base deficit >5 mEq/L • Increased arterial lactate: >2 times upper limit of normal • Oliguria: urine output <0.5 mL/kg/hr • Prolonged capillary refill: >5 sec • Core to peripheral temperature gap >3°C (5.4°F) 2. ARDS as defined by the presence of a PaO_2/FIO_2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure or Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)
Septic shock	Sepsis plus cardiovascular organ dysfunction as defined above
MODS	Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

Ref : Nelson Textbook of pediatrics, 20th Edn

INCIDENCE AND ETIOPATHOGENESIS:

Bone et al in 1997 proposed a new hypothesis for pathogenesis of the disease process of sepsis, which put forth the idea that the initial inflammatory response gave way to a subsequent "compensatory anti-inflammatory response syndrome"(7). The infection triggers a much more complex, variable and prolonged host response, in which both pro-inflammatory and anti-inflammatory mechanisms can contribute to clearance of infection and tissue recovery on one hand and organ injury and secondary infections on the other(7). The pro-inflammatory reactions are responsible for collateral tissue damage, whereas the anti-inflammatory responses are implicated in the enhanced susceptibility to secondary infections(3).

In the United States, severe sepsis is recorded in 2% of all patients admitted to the hospital. Half of these patients are treated in the intensive care unit, representing 10% of all ICU admissions(4). Adhikari et al in a study done in adults on critical care and the global burden of critical illness estimated the incidence rates of sepsis in the United states as upto 19 million cases worldwide per year. Severe sepsis occurs as a result of both community-acquired and health care-associated infections. Blood cultures are typically positive in only one third of cases, and in upto a third of cases cultures from all sites are negative. An epidemiologic study of sepsis showed that during the period from 1979 to 2000, gram –positive infections overtook gram-negative infections (6). However in a more recent study done by Vincent et al in 2009 about the prevalence and outcome of infection in intensive care units involving 14,000 ICU patients in 75 countries done in

adults, gram-negative bacteria was isolated in 62% of patients with severe sepsis, gram-positive bacteria was isolated in 47% and fungi in 19%.(9)

Risk factors for sepsis are related both to a patient's predisposition for infection and to likelihood of acute organ dysfunction if infection develops (10). The well known risk factors that most commonly precipitate severe sepsis and septic shock include age, sex, race, ethnicity, chronic diseases like acquired immunodeficiency syndrome, other co-morbidities like- cardiovascular, hematologic/immunologic, malignancy, post solid organ/stem cell transplant(10).

Schlapbach et al in a multicentre retrospective cohort study done between 2002-2013, about the mortality related to invasive infections, sepsis and septic shock in critically ill children in Australia and New Zealand, showed that the factors significantly associated with mortality in pediatric sepsis were oncological conditions (OR 1.95, 95% CI 1.41-2.69), cardiovascular conditions(OR 1.41, 95% CI 1.33-1.50), bone marrow transplantation (OR 2.80, 95% CI 1.76-4.44), chronic neurological disorder (OR 1.76, 95% CI 1.23-2.52), chronic renal failure (OR 3.22, 95% CI 1.43-7,24)(10) . The mortality rate was however highest in children with solid organ/stem cell transplant (48.2%), followed by malignancies (41.3%), renal diseases (38.2%), hematologic/immunologic conditions (37.7%). This study also showed that the most common sites of infection are respiratory tract (57.2%) and bloodstream infections (67.8%).(11)

Children less than 12 months have the highest risk of death from blood stream infections. Indwelling vascular lines, urinary catheters, endotracheal tubes and other foreign materials further predispose already compromised children to nosocomial infections.(12) Certain organisms are associated with poor prognosis, particularly fungi, infections with antibiotic resistant bacteria and hospital-acquired pathogens. Ruth et al in a multicentre database study done from 2002 to 2012, on the current trends and outcomes from the pediatric health information systems database stated that the proportion of severe sepsis in children with at least one co-morbidity has been increasing from 64.9% in 2002 to 76.6% in 2012 ($p<0.0001$).(13)

ORGAN DYSFUNCTION IN SEPSIS:

Organ dysfunction is the presence of altered organ function such that the homeostasis cannot be maintained without intervention. The criteria to diagnose organ dysfunction in infants and children were first described by Proulx et al in 1996 and updated in 2005 by Goldstein et al.

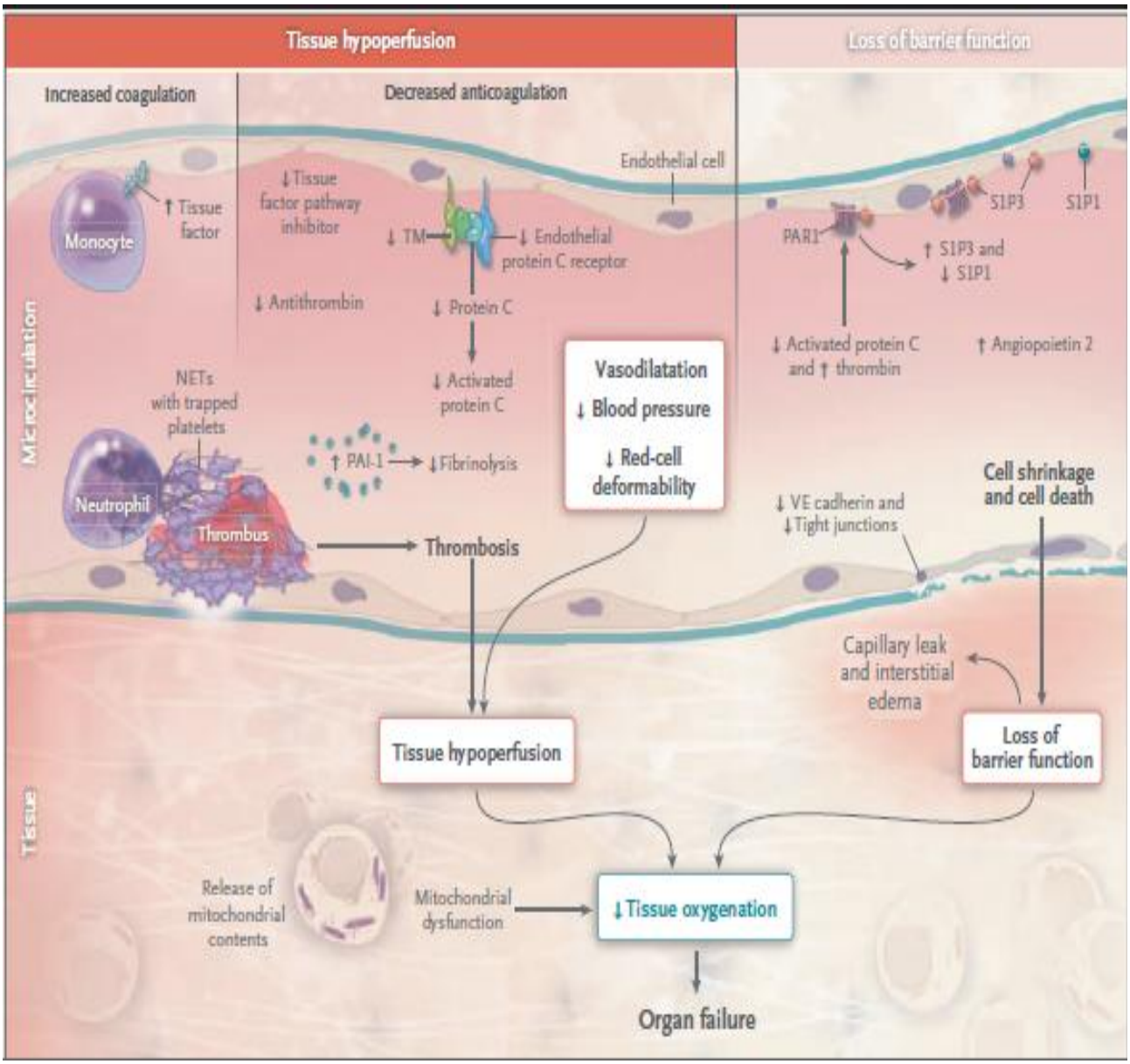
The organ-dysfunction variables include arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300), acute oliguria (urine output <0.5ml/kg/hr), increase in creatinine level of > 0.5mg/dl, coagulation abnormalities (INR >1.5, APTT>60 secs), paralytic ileus (absence of bowel sounds), thrombocytopenia (platelet count <1,00,000/mm^3) and hyperbilirubinemia (total bilirubin >4mg/dl).(14)

Although the **mechanisms** that underlie organ failure in sepsis have been only partially elucidated, impaired tissue oxygenation plays a key role. Several factors – including hypotension, reduced red-cell deformability and microvascular thrombosis –contribute to diminished oxygen delivery in septic shock. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema. (16)

In addition mitochondrial damage caused by oxidative stress and other mechanisms impairs cellular oxygen use. Moreover injured mitochondria release alarmins into the extracellular environment, including mitochondria DNA and formyl peptides, which can activate neutrophils and cause further tissue injury.(17)

The factors which account for **poor prognosis** in children with septic shock include time lag to PICU transfer, length of PICU stay, presence of multi-organ dysfunction, poor paediatric risk of mortality score at admission, prediction of patient outcome at admission to PICU is not only important in counseling parents but also for the optimum utilization of limited resources. (18)

FIGURE 1.THE ORGAN FAILURE IN SEVERE SEPSIS AND DYSFUNCTION OF THE VASCULAR ENDOTHELIUM AND MITOCHONDRIA :



Ref : N ENGL J MED 369;9 august 29, 2013

Many studies have analysed risk factors for death in various clinical syndromes associated with septic shock. Despite appropriate therapy in many circumstances, the multiple organ dysfunction syndrome develops in many cases. In this

syndrome, there is variable involvement of many organs, such as ongoing shock from cardiovascular dysfunction, acute tubular necrosis, respiratory failure, hepatic dysfunction, encephalopathy and coagulopathy.(19) Studies reveal that non survivors of sepsis had significantly marked derangement of renal, hepatic and coagulation profile, higher requirement of inotropes and larger number of multiple organ dysfunction and are important risk factors for mortality in combination.

MODS SCORE IN ICU:

Several scoring systems for measuring Paediatric MODS have been described in the literature which include PRISM (Paediatric risk of mortality), PELOD (Paediatric logistic organ dysfunction), PIM (Paediatric index of mortality), PEMOD (Paediatric multiple organ dysfunction) scores. PELOD score has been validated in a multi-centre study, risk of mortality was directly proportional to the degree of organ dysfunction and the score increased with each organ dysfunction. The PELOD score has 12 variables and six organ dysfunctions, and the most abnormal value each day was used to calculate the score. The AU-ROC curve ranged from 0.79 to 0.85 during the first 5 days and the discrimination was 0.91 ±0.01 which was quite good.

PELOD score was **significantly higher in non-survivors than in survivors** and there was a significant correlation of the score with mortality. Marshal and colleagues put forth the approach to create and validate the multiple organ

dysfunction score, which has been put forward for inclusion in the assessment of sepsis.

TABLE 2. PEDIATRIC LOGISTIC ORGAN DYSFUNCTION SCORE:

Organ dysfunctions and variables[a]	Points by severity levels						
	0	1	2	3	4	5	6
Neurologic[b]							
Glasgow coma score	≥11	5-10			3-4		
Pupillary reaction	Both reactive					Both fixed	
Cardiovascularc							
Lactatemia (mmol/L)	<5.0	5.0-10.9			≥11.0		
Mean arterial pressure (mm Hg) (months)							
0-<1	≥46		31-45	17-30			≤16
1-11	≥55		39-54	25-38			≤24
12-23	≥60		44-59	31-43			≤30
24-59	≥62		46-61	32-44			≤31
60-143	≥65		49-64	36-48			≤35
≥144	≥67		52-66	38-51			≤37
Renal							
Creatinine (µmoL/L) (months)							
0-<1	≤69		≥70				
1-11	≤22		≥23				
12-23	≤34		≥35				
24-59	≤50		≥51				
60-143	≤58		≥59				
≥144	≤92		≥93				
Respiratory[d]							
PaO_2 (mm Hg)/FiO_2	≥61		≤60				
$PaCO_2$ (mm Hg)	≤58	59-94		≥95			
Invasive ventilation	No			Yes			
Hematologic							
WBC count (×10⁹/L)	>2		≤2				
Platelets (×10⁹/L)	≥142	77-141	≤76				

[a]All variables must be collected, but measurements can be done only if justified by the patient's clinical status. If a variable is not measured, it should be considered normal. If a variable is measured more than once in 24 h, the worst value is used in calculating the score; [b]Neurologic dysfunction - Glasgow coma score: Use the lowest value. If the patient is sedated, record the estimated Glasgow coma score before sedation. Assess only patients with known or suspected acute central nervous system disease. Pupillary reactions: Nonreactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation; [c]Cardiovascular dysfunction: Heart rate and mean arterial pressure: Do not assess during crying or iatrogenic agitation; dRespiratory dysfunction: PaO_2: Use arterial measurement only. PaO_2/FiO_2 ratio is considered normal in children with cyanotic heart disease. $PaCO_2$ can be measured from arterial, capillary, or venous samples. Invasive ventilation: the use of mask ventilation is not considered invasive ventilation. Logit (mortality) = −6.61 + 0.47 × PELOD-2 score; Probability of death = 1/(1 + exp [− logit (mortality)]); FiO_2: Fraction of inspired oxygen; PELOD: Pediatric logistic organ dysfunction; PaO2: Arterial oxygen pressure; WBC: White blood cell

Ref: The lancet 2003-validation of the PELOD score

SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY:

Acute kidney injury is a frequent and serious complication of sepsis in intensive care unit (ICU) patients as per Lafrance et al in a study done in ICU set-up in 2010 on acute kidney injury associates with increased long-term mortality. There is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients account for 50% or more cases of AKI in ICUs and associate with a very high mortality.

It is well established that kidney is a commonly affected organ during sepsis, and its involvement carries a high risk of mortality. The patho-physiology of AKI in sepsis is complex and multi-factorial and includes intrarenal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells in the renal parenchyma, intra-glomerular thrombosis and obstruction of tubules with necrotic cells and debris. A growing evidence now suggests that sepsis-associated immune responses involve the activation, in a sequential manner, of both pro and anti-inflammatory mechanisms.

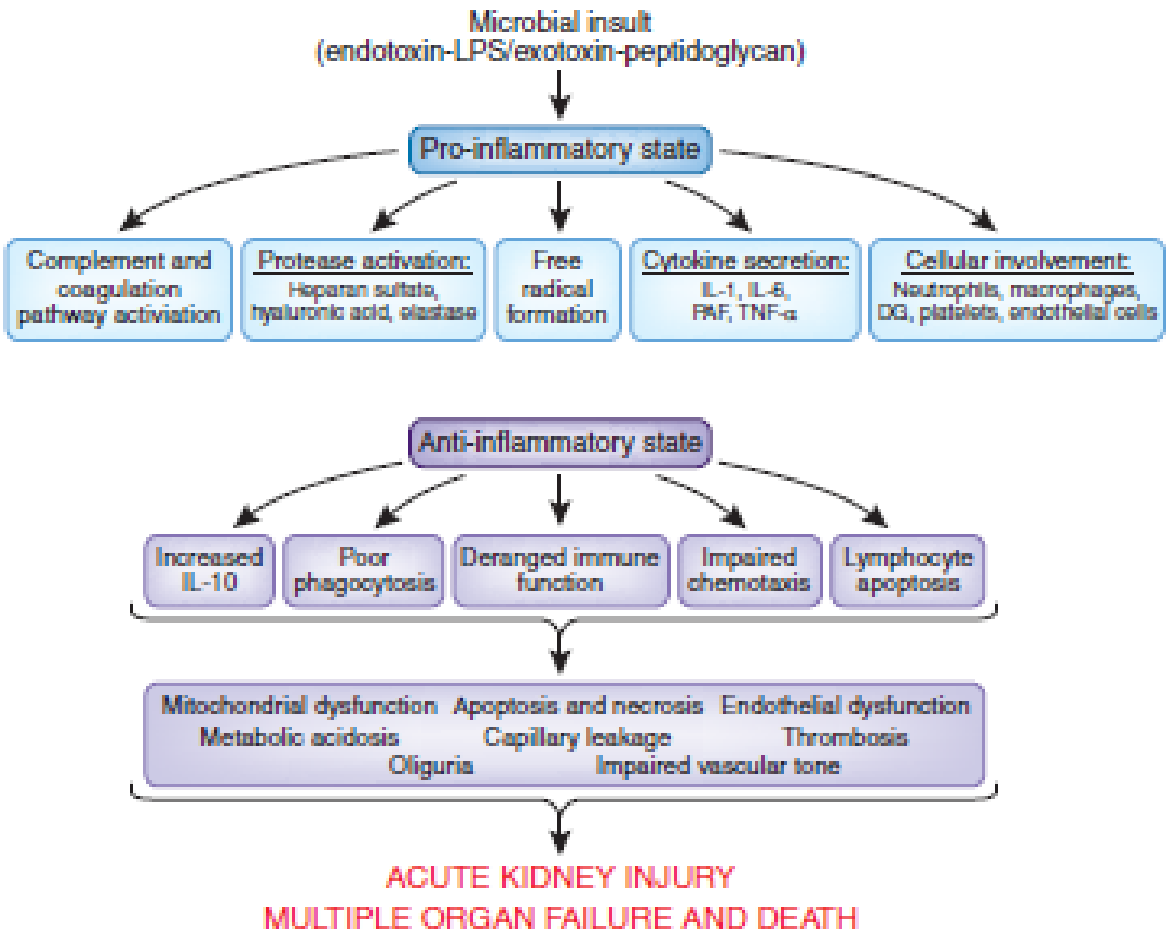
After initial host-microbial interaction, there is wide-spread activation of innate immune response, which co-ordinates a defensive response involving both humoral and cellular components. This in turn leads to secretion of various cytokines, most importantly IL-1, TNF-α, IL-6 that progress to a state of cytokine storm, hemodynamic instability, and eventually organ dysfunction and septic shock. (20)

This pro-inflammatory phase is followed by a compensatory anti-inflammatory response; an immunosupressed state characterized by altered cytokine production and antigen presentation by monocytes, decreased lymphocyte proliferation and increased apoptosis. Recent studies suggest an anti-inflammatory role for soluble thrombomodulin in AKI and release of stem cell factor by MMP-9 has an anti-apoptotic effect through activation of cKit. (22)

Toll like receptors (TLR) are a class of proteins that play an important role in altering the innate immune system. Modulation of TLRs may become a novel therapeutic target especially in the treatment of organ injury accompanying sepsis. Arterial vasodilatation with an associated decrease in systemic vascular resistance is a fundamental hallmark of sepsis. (25)

The characteristic pattern of renal blood flow (RBF) in human sepsis is for the most part largely unknown because RBF cannot be measured continuously in humans, and even its intermittent measurement requires a high level of invasiveness. Afferent and efferent arterioles are essential regulators of renal perfusion. Simultaneous dilation of both arterioles can lead to decreased glomerular capillary pressure and subsequent decrease in filtration. This is very similar to the observed effects of angiotensin-converting enzyme inhibitors and may account for the AKI that accompanies sepsis.

FIGURE 2.SHOWS THE KEY PATHOGENIC PATHYWAYS IN SEPSIS INDUCED AKI



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ournal of the American society of Nephrology 22:99-106, 2011

BIOMARKERS IN SEPIS-ASSOCIATED AKI:

Septic AKI is characterized by a distinct pathophysiology and important differences exist in patient characteristics, response to interventions and clinical outcomes. This may also extend to unique patterns of plasma and urinary biomarkers in septic AKI. For instance the excretion of IL-18 is higher in septic AKI than in non septic AKI. The increased level

of IL-18 predicts deteriorating kidney function approximately 24 to 48 hours before clinically significant AKI(24). Moreover sepsis decreases production of creatinine without major alterations in body weight, hematocrit or extracellular fluid and creates further limitations on using changes in creatinine levels as a reliable marker of AKI. Hence it is essential to have markers that enable early detection of AKI. The utility of these novel biomarkers including Cystatin C, Neutrophil gelatinase –associated lipocalin, Liver type fatty acid binding protein, netrin-1 for early detection of sepsis-induced AKI is very encouraging and may have prognostic implications as well.(28)

For instance urinary liver type fatty acid-binding protein (L-FABP) is significantly higher in AKI associated with sepsis than in non-AKI in adult ICU patients as per study done by Nakamura et al on urinary liver-type fatty acid binding protein in septic shock in 2009 which was a prospective cohort study in adult ICU patients.

L-FABP has been shown to detect renal injury earlier than creatinine and also predicts mortality and poor outcome in children with severe sepsis as per Doi et al, in his prospective observational study in post-surgical patients in ICU with AKI done in 2010.

Table 3.LIST OF EMERGING BIOMARKERS-IN SEVERE SEPSIS:

Biomarker	Source of Sample	Elevation in Sepsis-induced AKI
Cystatin C	Plasma	Intermediate
L-FABP	Urine	Early
IL-18	Urine	Intermediate
NGAL	Plasma	Early
KIM-1	Urine	Intermediate
Netrin-1	Urine	Early

L-FABP, L-type fatty acid–binding protein; NGAL, neutrophil gelatinase-associated lipocalin; K kidney injury moleclue-1.

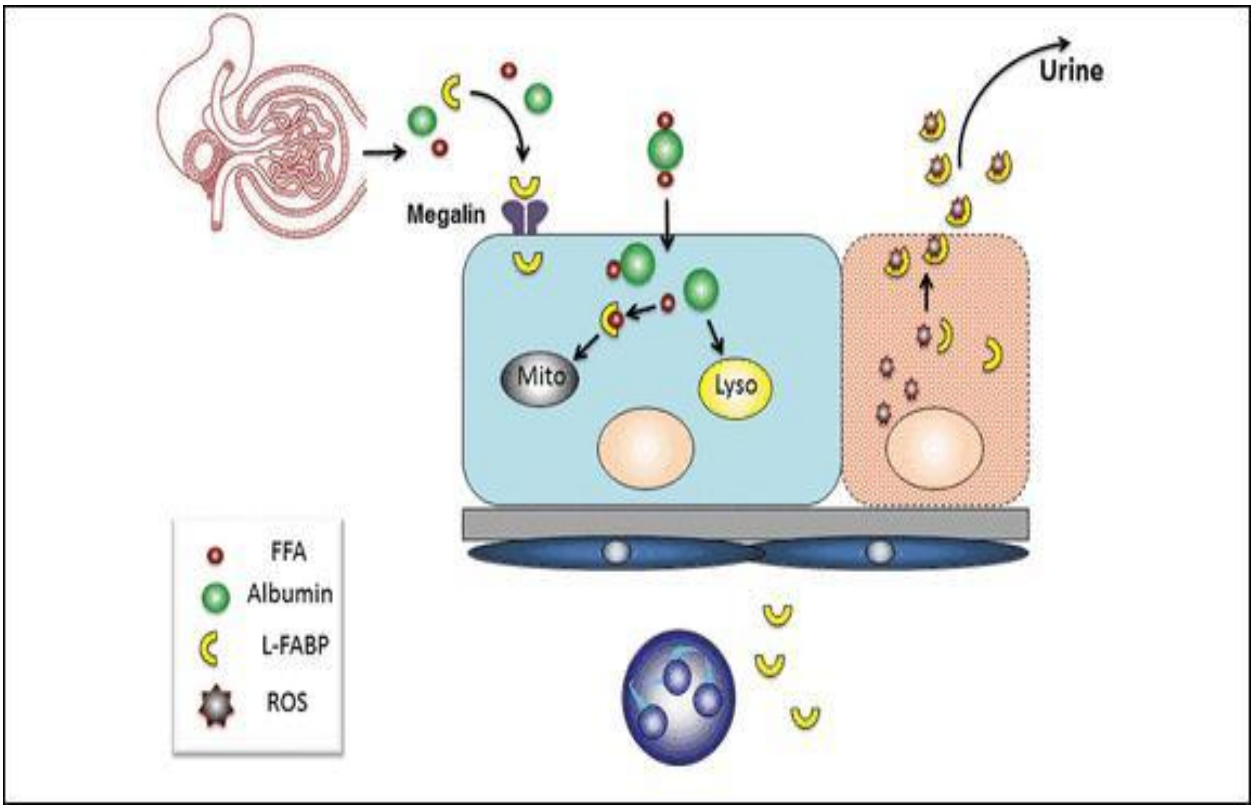
Ref : J Am Soc Nephrol 22 :999-1006, 2011

LIVER TYPE FATTY ACID BINDING PROTEIN (L - FABP):

Liver-type fatty acid binding protein(L-FABP), one such candidate biomarker, which is a 14kDa protein, is expressed in the proximal tubular epithelial cells, hepatocyte and crypt to villus tip of intestine. This endogenous antioxidant promotes free fatty acid metabolism by binding long-chain fatty acid oxidation products. L-FABP is bound to serum albumin and is reabsorbed into proximal tubule bound to serum albumin. Filtered L-FABP is taken up proximal tubule and acts as a carrier protein and transports free fatty acids to mitochondria and peroxisome for metabolism.

Upon stress and ischemia-reperfusion injury there is an upregulation of L-FABP, which binds lipid hydro-peroxides and other reactive oxygen species which together is released into urine(30).

FIGURE 3.SHOWS THE SITE OF SECRETION OF L-FABP:



Ref:L-FABP and kidney disease 2014

Urinary L-FABP could serve as a biomarker of AKI primarily in septic patients presenting with shock and multiorgan failure, in whom the potential for liver involvement could be present. Once in the proximal tubular cells, L-FABP may act as a

surrogate molecule to reduce lipid peroxidative stress during reperfusion by binding fatty acid oxidation products and limiting the toxic effects of oxidative intermediates on cellular membranes. L-FABP not only contributes to the trafficking of fatty acids but also serves as a diagnostic indicator of acute renal diseases.

ACUTE KIDNEY INJURY CRITERIA:

Recognition of AKI requires the delineation of easily measured criteria that can be widely applied. In September 2005, in a meeting in Amsterdam a new classification of AKI was proposed by the acute kidney injury network (AKIN) working group composed of nephrologists, critical care physicians and other physicians specialized in AKI. The AKIN classification was published in March 2007 in critical care, the diagnosis of AKI is considered only after achieving adequate status of hydration and after excluding Urinary obstruction. AKIN classification only relies on serum creatinine and not on GFR changes, baseline serum creatinine is not necessary and it requires at least two values of serum creatinine obtained within a period of 48 hours. It gives important information about the etiological diagnosis. AKIN classification allows identification and stratification of AKI in a large proportion of hospitalized patients and was

independently associated with the outcome. Patients with AKI had higher in-hospital mortality and longer lengths of stay, AKI survivors were more likely to be discharged to an extended care facility. (35)

The Acute dialysis quality initiative (ADQI) group for the study of AKI proposed the criteria for defining AKI, which was the pRIFLE (pediatric risk, injury, failure, loss and end stage renal disease) in may 2004. pRIFLE is based on serum creatinine and urine output determinants, it has largely been validated in terms of determining the incidence of AKI and its prognostic stratification in several settings of hospitalized patients. However it has a number of limitations, since baseline creatinine is necessary to define and classify AKI , which is frequently unknown in clinical practice.(38)

Hence to overcome the practical difficulties, in September 2005 a new classification of AKI was proposed by the Acute Kidney Injury Network (AKIN) working group. The AKIN classification which was published in march 2007, in which baseline serum creatinine is not necessary in the AKIN classification. It requires at least 2 values of creatinine obtained within a period of 48 hours.(40)

TABLE 4. AKIN CRITERIA:

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline or ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hours
2	2-2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline or Initiation of renal replacement therapy or In patients < 18 years, decrease in eGFR to < 35 ml/ min per 1.73 m2	< 0.3 ml/kg/h for ≥ 24 hours or Anuria for ≥ 12 hours

5

AKIN classification allows the identification and stratification of AKI in a large proportion of patients and was independently associated with outcome. This classification adds important etiological information. The integration of the new biomarkers of AKI into the clinical classification could increase the sensitivity and specificity of AKI diagnosis.

Renal replacement therapy:

Renal support therapy has been used for treatment of sepsis associated acute kidney injury. Timing of initiation of renal replacement therapy is highly controversial, data suggest initiation of therapy before onset of overt complication and accumulation of significant fluid overload which may lead to improved survival. The ideal modality to support critically ill patients is still unclear. Continuous renal replacement therapy (CRRT) is used most commonly in critically ill unstable patients because of its adaptability to patient condition and better physiologic and hemostatic control. Data suggest the early initiation of renal replacement therapy may facilitate better renal recovery and reduce long term risk of chronic kidney disease. CRRT possesses several distinct advantages over peritoneal dialysis and hemodialysis in the management of sepsis associated acute kidney injury. CRRT mimics the effects of renal function with its continual ultra filtration and solute clearance. It can deliver prescribed ultra filtration rates unlike peritoneal dialysis. Hence this makes CRRT preferable for provision of renal supportive therapy as compared to other modalities especially in hemodynamically unstable fluid overloaded septic patients. Adequate nutritional delivery is possible with

CRRT since there is no need for fluid restriction and ultrafiltration rates can be adjusted concomitantly with increased volume infusions associated with increased nutritional delivery. CRRT has additional benefit of restoring immunohemostasis by removing both proinflammatory and anti-inflammatory molecules during sepsis associated acute kidney injury. Children with AKI and sepsis are often at risk for undernutrition. Renal supportive therapy can lead to loss of free amino acids and peptides thereby leading to negative nitrogen balance. Fluid restriction exacerbate the above condition by further contributing to undernutrition. This may lead to reduced survival rates. CRRT has been used as a technique to deliver 100% recommended daily allowance either by enteral or parenteral nutrition. (42)

A multinational study done in 2000 by Uchino et al showed that acute renal failure accounts for about 5.5 to 6% of all admissions to pediatric intensive care unit. Of the various causes septic shock accounted for 47.5%, major surgery 34%, cardiogenic shock 25%, hypovolemia 26%, nephrotoxins 19%. Sepsis-associated AKI occurs in approximately 20% of patients with moderate sepsis and 50% in septic shock when blood cultures are positive. Opera et al in a German prevalence study on acute renal failure in patients with severe sepsis found a prevalence of 41.4%. (35)

Bailey et al in a prospective study to determine the incidence, risk factors and outcome of acute renal failure in critically ill children in a tertiary pediatric intensive care unit in

Canada noted an AKI incidence rate of 4.5%. The most common diagnoses causing acute kidney injury were hemolytic uremic syndrome (18.2%), oncologic pathologies (18.2%) and cardiac surgery (11.4%).

Medlina et al in a prospective study performed in 4 PICUs in Spain among children aged 7 days to 16 years noted the incidence of acute kidney injury to be 2.5%. Bresolin et al studied 110 critically ill children admitted between 2002 and 2004 to an intensive care unit in Brazil and had acute kidney injury to define poor prognostic factors in critically ill children. Thus an incidence of acute injury of 8% was noted in this study.

Renal ischemia (21%) and sepsis (11%) were major causes of acute kidney injury in a retrospective study done in USA by Stickle et el on 248 children with acute kidney injury.

In another retrospective study done by Agarwal et al in Christian Medical College, Vellore, among south Indian children, to assess the clinical profile of children admitted with acute renal failure and to identify factors associated with poor outcome, 54 children between one month and 12 years with acute renal failure were studied. Amongst the various precipitating causes of renal failure, proven sepsis was found in 22% of the children. Mortality due to sepsis was 83%, of which mortality was 65% in patients who were on dialysis and 100% in those requiring ventilator support.

Khilnani et al in his prospective observational study on the profile and outcomes of children admitted to a tertiary intensive care unit in India between January 1998 and December 2000, found the incidence of multi-organ dysfunction to be 18-25%. In the same study it was reported that diagnosis of various patients included (respiratory19.7%, cardiac 9.7%, neurological 17.9%, infections 12.5%, trauma 11.7%, other surgical 8.8%. He found the incidence of nosocomial infections to be 16.86%. Multi-organ failure remained the major cause of death according to this study and dengue and malaria were the common infections. (45)

Gurpreet et al, Nikhil et al did a study on clinical outcome and predictors of mortality in children with sepsis, severe sepsis and septic shock which was a prospective observational study done in children aged one month to 14 years admitted to a tertiary care PICU in Rohtak, Haryana between November 2012 and February 2013. Hemodynamic and laboratory parameters which discriminate survivors from nonsurvivors were evaluated. A total of 50 patients were enrolled in the study of whom 21(42%) were discharged (survivors) and rest 29(58%) expired (nonsurvivors). Duration of ICU stay (OR 95% CI: 1.18(0.99-1.25), time lag to PICU transfer (OR 95% CI: 1.02(0.93-1.12), number of organ dysfunction (OR 95% CI: 0.03(0.01-1.53) p=0.08). This study stated that mortality among children with sepsis, severe sepsis and septic shock were not predicted by any individual factors including time lag to PICU transfer, duration of stay, presence of multi-organ dysfunction.

The **SPROUT (**The Sepsis Prevalence, outcomes and Therapies) study was a prospective cross-sectional study conducted in children less than 18 years with severe sepsis in PICUs across the world at 128 sites in 26 countries on 5 days throughout 2013-2014. Out of 6925 patients screened, 569 had severe sepsis (prevalence 8.2%, 95% CI:7.6-8.9%). This study showed that the most common sites of infection being respiratory (40%) and blood stream (19%). Common therapies included mechanical ventilation (74% patients), vasoactive infusions (55%), corticosteroids (45%). Hospital morality was 25% and did not differ by age or between developed and resource-limited countries. Median ventilator-free days were 16(IQR 0-25), vasoactive free days were 23(IQR 12-28). 67% of patients had multi-organ dysfunction at sepsis recognition, with 30% subsequently developing new or progressive multiorgan dysfunction. Among survivors 17% developed at least moderate disability. This large international study demonstrates that pediatric severe sepsis remains a highly prevalent public health problem in critically ill children and is associated with substantial morbidity and mortality.

In a prospective observational study done in PICU of Cairo university, Mounira Pediatric hospital over one year which included 231 patients, to assess the severity of diseases and predicting mortality in ICUs by using scoring systems, the mortality rate was 6.4%-10.3% in critically ill patients. There were positive correlations between PRISM III, PIM2, PELOD, PEMO D , SOFA and TISS scores on the day of admission and mortality rate ($p<0.0001$).(45)

This study showed that risk of mortality was elevated in patients on inotropes (OR-8.5). Also insertion of central venous line reflected severity of the case because risk of mortality was elevated (OR=6.9). Mortality was high in patients with liver enzymes >250IU/L(OR-3.6; ALT 95% CI: 47.86-155; AST 95% CI 74.96-395.28), elevated bilirubin >6mg/dl (OR=12.8; 95% CI: 1.93-12.1)and low albumin (OR=4.4; 95% CI :3.1- 3.39). There was a significant relation between blood urea nitrogen and mortality (p=0.01). The highest risk of mortality was found with serum creatinine >5mg/dl (OR= 17 and specificity 98.8; 95% CI: 0.67 -1.29). Risk of mortality increased with low platelet count ranging from 1,00,000 to 1,49,000 (OR=3.7; 95% CI: 276.21-371.26). Mortality doubled in patients with PT >22s or PTT > 57s (OR=6.5; PT 95% CI: 20.22-42.67; PTT 95% CI: 39.69-132.58) and was 100% in patients who needed anti-coagulation treatment (those patients of post-cannulation thrombosis).

Risk of mortality was high in patients with potassium >8meq/L (OR= 12.1; 95% CI:4.08-4.91) or calcium from 5 to 6.9 mg/dl (OR= 5.5; 95% CI: 8.17-9.03). Risk of mortality increased in patients with metabolic acidosis (OR=12.7; specificity 97.7; pH 95% CI : 7.2-7.33), fever and hypothermia (OR = 5.9; specificity 99.4) and patients who required more than one peripheral line (OR=6; specificity 84.4). Persistent shock on admission to ICU is associated with increased odds ratio for death 3.8. For every hour of persistent shock, the odds ratio for death was 2.29 (95% CI:1.19 to 4.44).

With treatment the overall mortality is approximately 10% in children upto 19 years of age as per a study done in PICU in Birmingham children's hospital UK , by Adrian Plunkett and Jeremy Tong between October 2008 to October 2013. Patients with pre-existing disease experience a higher mortality of 12.8% compared with 7.8% in previously healthy children. (45)

The Beginning, Ending Supportive Therapy for the Kidney, a large prospective observational study of more than 29,000 patients in ICU at 54 hospitals in 23 countries across the world, from September 2000 to December 2001, in patients >12 years of age, to characterize differences in etiology, illness severity and clinical practice, reported an AKI incidence of 5.7%, with SA-AKI being the highest associated etiology (47.5%). Overall mortality was 60.3% (95% CI 58-62.6%). This study showed that the most common contributing factor to ARF was septic shock (47.5% 95%CI :58.0-62.6%). Dialysis dependence at hospital discharge was 13.8% (95% CI 11.2-16.3%) for survivors. Independent risk factors for hospital mortality include use of vasopressors (OR1.95 95% CI: 1.50-2.55, $p<0.001$), mechanical ventilation (OR

2.11, 95% CI 1.58-2.82, p<0.001), septic shock (OR 1.36 95% CI:1.03

1.79,P=0.03), cardiogenic shock (OR 1.41, 95%CI :1.05-1.90,p-0.02). (39)

This study showed that the major reason for ICU admission was medical in 58.9% and surgical in remaining 41.1%. Cardiovascular surgery was the most common diagnostic grouping, followed by medical respiratory, medical cardiovascular, gastrointestinal tract surgery and sepsis. While 50% of ARF patients died in ICU another 8% died in the hospital after discharge from ICU. Of the patients who survived to hospital discharge, 13.8% (95% CI: 11.2%-16.3%) required RRT at the time of discharge. The median length of ICU stay was 10days (IQR 5-22 days) and the median length of hospital stay was 22 days (IQR 11-44 days). Based on this research the world-wide prevalence of acute RRT was approximately 4%.

In a retrospective observational study done by Lopes et al JA in acute kidney injury in adults with sepsis in 2009, between Janunary 2004 and June 2007, a total of 315 patients were studied. According to AKIN criteria, 99 patients (31.4%) had AKI : 26.2% at stage 1, 20.2% at stage 2, 53.6% at stage 3. Four patients (1.9%) with no AKI progressed to stage 1, two patients (7.7%) at stage 1 progressed to stage 2, one patient (3.8%) at stage

1 progressed to stage 3, and one patients at stage 2 (5%) progressed to stage 3. The mortality rate was 25.3% and increased from normal renal function to stage 3 (normal 12.5%; stage 1, 34.6%; stage 2, 45%;stage 3, 64.1%; p<0.0001). The predicted mortality in various stages include AKIN stage 1 (OR 3.03, 95% CI: 1.12-8.19,p=0.029), stage 2 OR 3.3, 95% CI: 1.11-9.78,p=0.031) and stage 3 (OR 7.35, 95% CI: 3.13-17.25 , p<0.0001). Hence based on this study they concluded that AKIN criteria was a useful tool to characterize and stratify septic patients according to the risk of death.

In another retrospective study done by Agarwal et al among south Indian children, to 54 children between one month and 12 years with acute renal failure were studied. Amongst the various precipitating causes of renal failure, proven sepsis was found in 22% of the children. Mortality due to sepsis was 83%, of which mortality was 65% in patients who were on dialysis and 100% in those requiring ventilator support.

A retrospective study was done by Nakamura et al done in adults to determine whether urinary liver-type fatty acid binding protein levels altered in patients with septic shock or severe sepsis without shock among 40 cases and 30 controls in 2009, the results showed that the urinary L-FABP levels measured by ELISA method, were significantly higher in patients with septic shock(p<0.001), than in those without shock(p<0.05), patients with ARF (p<0.001), whereas serum L-FABP did not show any significant difference. Urinary L-FABP levels remained high for 7 days after initiation of conventional treatment (p=0.12). These results suggest that urinary L-FABP levels were significantly increased

in patients with septic shock. The sensitivity and specificity of L-FABP for diagnosing AKI as against hospitalized controls, showed a sensitivity of 83% and specificity of 90%.

In a cross-sectional study Ferguson et al studied the comparative values of multiple biomarkers used in the diagnosis of AKI. In a total of 92 patients with established AKI, they showed that the diagnostic ability of L-FABP in diagnosing AKI in hospitalized patients was very good **(ROC-AUC 0.93),** as compared to other well-described biomarkers of AKI including NGAL (0.92), KIM-1(0.89), NAG(0.89) and IL-18(0.83). In this study L-FABP emerged as a s**ignificant predictor of RRT (p=0.02)** and the composite **end point of death/RRT (p=0.03),** however in this study, urinary L-FABP did not predict in-hospital mortality (p=0.26).

In a prospective observational study conducted at the Dhaka hospital of International centre for Diarrhoeal Disease Research, Bangladesh, in children aged 6-59 months admitted with sepsis from April 2010 to December 2011, to study the utility of urinary L-FABP as a mortality predictor in <5 year old children with sepsis, showed that the first urine L-FABP ≥ 370ng/ml (RR 2.76 ;95% CI:1.22-6.25), was identified as a significant risk factor of mortality in children with sepsis. Diagnostic performance of first urine L-FABP was analysed using ROC-AUC and was found to be 0.647(95% CI: 0.500-0/795), which showed that urinary L-FABP may be a useful predictor of mortality in septic children. (44)

A meta-analysis of the performance of urinary liver-type fatty acid binding protein in acute kidney injury was studied in humans ,which included 15 prospective cohort and 2 case-control studies of which only 7 cohort studies were meta-analysed, the results were published in 2013 which estimated the **sensitivity of urinary L-FABP level for diagnosis of AKI as 74.5% (95% CI: 60.4%-84.8%), specificity was 77.6%(95% CI: 61.5-88.2%).** The estimated level of urinary **L-FABP for predicting dialysis requirement was 69.1%(95% CI:34.6-90.5%) and specificity was 42.7%(95% CI:3.1-94.5%),** for i**n-hospital mortality sensitivity and specificity were 93.2%(95% CI:66.2%-99.0%) and 78.8%(95% CI:27%-97.4%). (43)**

Although urinary L-FABP may be a promising biomarker for early detection of AKI and in-hospital mortality, its potential value needs to be validated in large studies and across a broader spectrum of clinical settings.(43)

CONCLUSION:

AKI is a significant clinical challenge for clinicians. Although sepsis associated AKI is a unique subset of all AKI, there is an incomplete understanding of its complex pathophysiology. SA-AKI contributes to a higher burden of morbidity and mortality in children with critical illness. Advancements have been made for development of robust and validated tools including discovery of novel biomarkers to enable early detection of renal injury for prevention and treatment of AKI.

METHODOLOGY:

Study design: This study is a prospective observational study

Setting: This study was undertaken in Child health department - Paediatric ICU/HDU, including paediatric wards, at Christian Medical college, Vellore, India.

Period of recruitment: Enrolment of study participants was done between January 2017 and August 2017. Enrolled patients were followed up during their entire period of admission.

Children of age 1 month to 19 years who were diagnosed with severe sepsis, who fulfilled the inclusion criteria and did not have any exclusion criteria, after appropriate written parental consent were included in the study.

Data collection:

Enrollment was done within 24 hours of admission. A case report form was filled which included their demographic details, clinical history and physical examination. On enrolment, a urine specimen was collected for L-FABP measurement. The daily clinical progress was monitored which included monitoring of urine output, clinical parameters, need for ventilation, inotropic support, blood products support and other complications.

The biochemical and laboratory parameters done every day was also recorded in the case report form which included daily monitoring of creatinine as well. Repeat urine L-FABP was collected after 48 hours of admission. The PELOD score (Paediatric logistic organ dysfunction) which assess the severity of organ dysfunction was done every day for the first 5 days or till the time of recovery whichever was earlier. The progress was recorded in the case report form. Urine L-FABP assay was done at admission and at 48 hours. Around 5ml of urine was collected in a container and was stored below -20°c for analysis. A commercial ELISA kit (Hycult Biotech, USA- Cat # HK 404-01) was used to process samples following the manufactures's instructions. The levels are expressed in pg/ml.

Participants:

Inclusion criteria: Diagnosis of severe sepsis as per **International Pediatric sepsis consensus conference :**

The criteria for severe sepsis include :

Sepsis- Systemic inflammatory response syndrome + evidence of suspected/proven infection

SIRS – 1. Tachycardia – HR > 2SD above normal for age

2. Tachypnoea – RR >2 SD above normal for age or need for mechanical ventilation

3. Abnormal temperature – Fever (>38.5 ^{o}C) or hypothermia (<36 ^{o}C)

4. Abnormal leucocyte profile

The operational definition of **severe sepsis** modified for our study included :

SIRS with evidence of infection (suspected/proven) and requirement of inotropic support after administration of 2 fluid bolus.

Exclusion criteria:

- Children who did not fulfill study criteria
- Children with pre-existing renal disease

Variables:

The data entry was done using Epidata and data analysis was be carried out using SPSS16.0. Descriptive statistics was be reported using Frequency and Percentage for categorical variable as sex, gender etc. Continuous variables were reported using Mean ± SD. Categorical variables were analyzed using Chi square /Fisher exact test. Two independent sample t test were done for comparing Continuous variables after checking

for normality.

Data sources/ measurement:

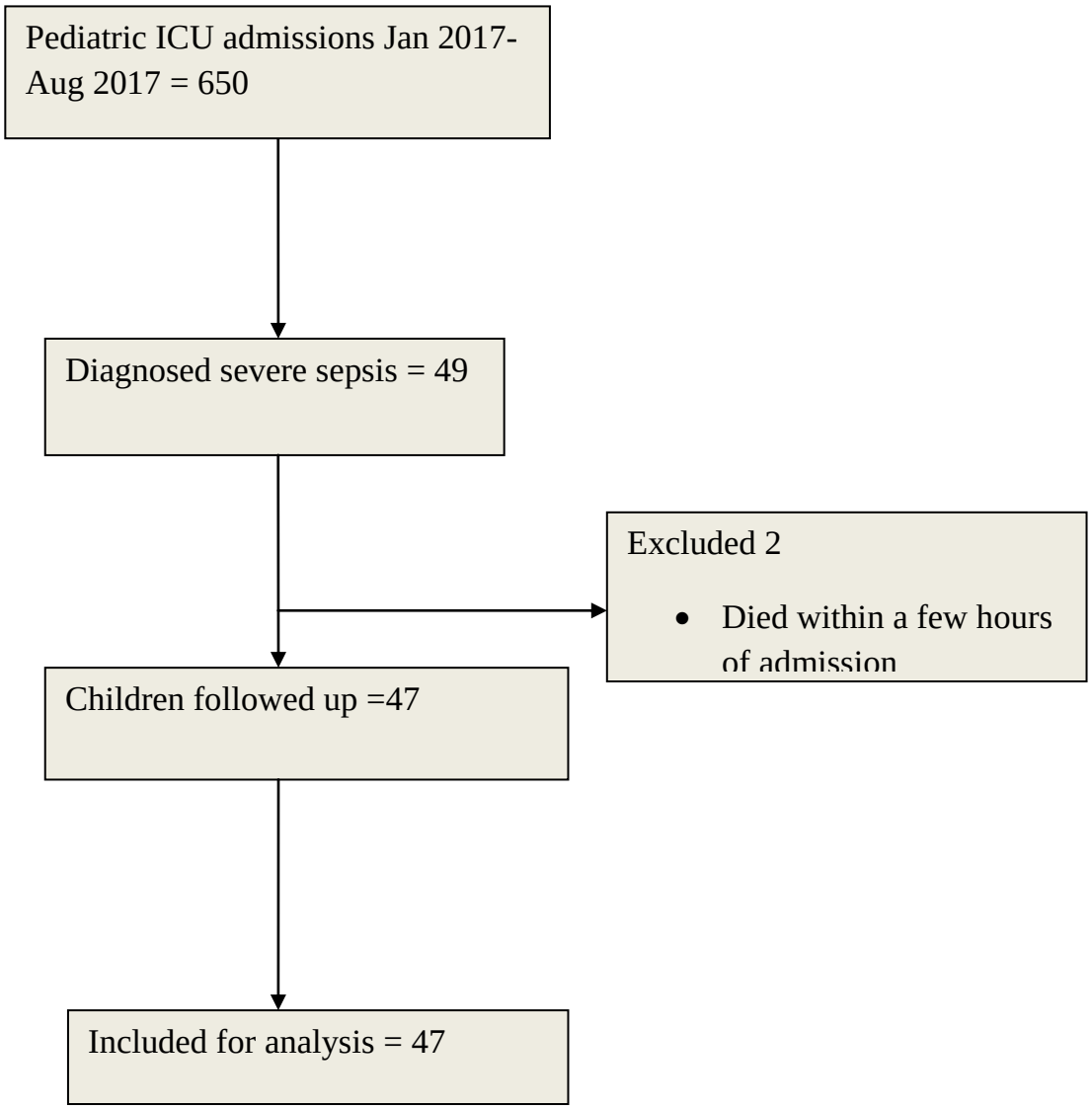
The variables to be noted and analyzed are given in the case report form. The data source for clinical information was taken from the medical record of the patient (i.e. in patient record or from Clinical work station). The L-FABP ELISA was be done as part of the study in the Nephrology lab and analysis obtained from there.

Study size:

The sample size is based on the prevalence of sepsis which includes cases with both AKI and Non-AKI –

Single Proportion - Absolute Precision	
Expected Proportion	0.3
Precision (%)	10
Desired confidence level (1- alpha) %	95
Required sample size	**61**

STROBE DIAGRAM :



RESULTS:

There were 650 admissions to the Pediatric Intensive care unit during the study period between January 2017 and August 2017.

Of these, 47(7.2%) had severe sepsis. These formed the study group which was evaluated further.

Of the 47 children with severe sepsis, 25/47(53.1%) had AKI. Two were excluded from analysis as they died within a few hours of admission and hence could not be followed up.

DEMOGRAPHIC DATA:

The profile of the study group based on age, sex and domiciliary distribution is given below.

CHARACTER	NUMBER n=47	PERCENTAGE(%)
1.Age 1-5 years	22	46.8
10-15 years	9	19.1
5-10 years	8	17
<1 year	6	12.7
>15 years	2	4.3
2.Sex		
Male	24	51.1
Female	23	48.9
3.Domicile		
Tamil Nadu	36	76.6
Andhra Pradesh	6	12.8
Other states	5	10.6

TABLE 1. DEMOGRAPHY

Majority of the children were between 1-5 years (22/47- 46.8 %) followed by 9/47 - 19.1% in the 10-15 year age group.

There were 24 males (51.1 %) and 23 Females (48.9%) M:F was 1:1.

Majority of the patients were from the state of Tamil Nadu 36/47 (76.1%)

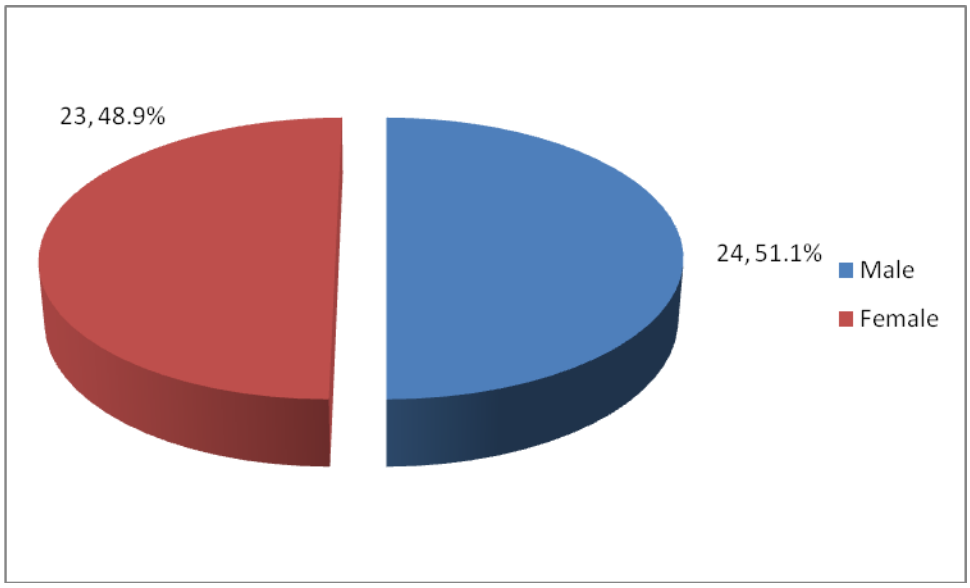


FIGURE 1.1

Among 47 children, 24 were males(51.1%) and 23 were females(48.9%)

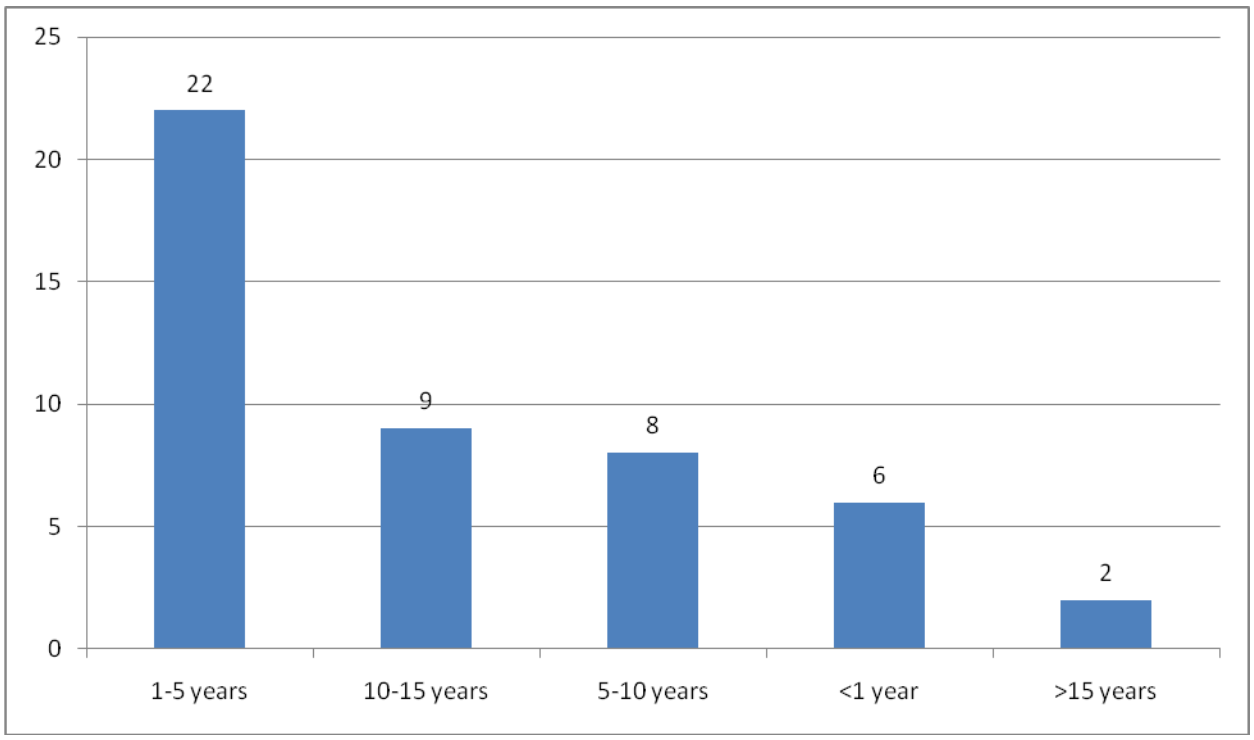


FIGURE 1.2

Among 47 children with Severe sepsis, 6(12.8%) were under 1 year of age

Majority of children were between 1- 5 years of age – 22/47 (46.8%)

Between 5-10 years there were 8/47(17%)

Between 10-15 years there were 9/47 (19.1%) and 2/47 were >15 years (4.3%).

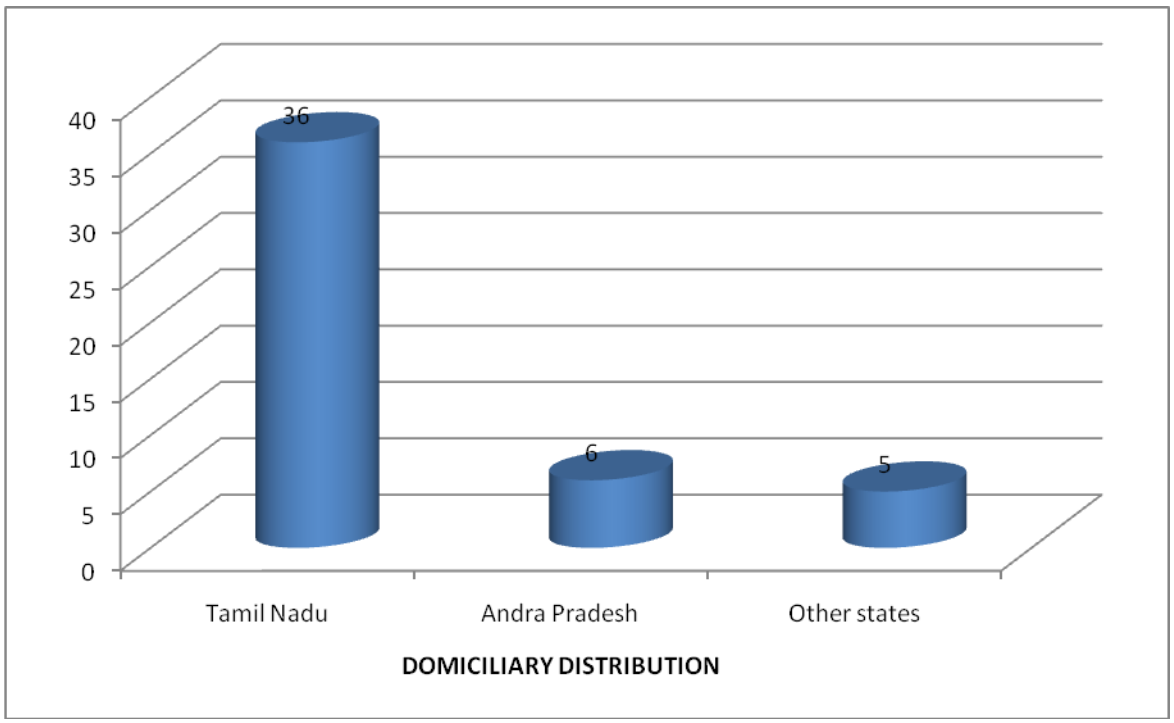


FIGURE 1.3

More than half of the population (36/47) were fom Tamil Nadu(76.6%); 6/47 (12.8%)were from Andhra Pradesh while 5/47 (10.6%) were from other states.

SYMPTOMATOLOGY AT PRESENTATION:

CHARACTER	NUMBER(n=47)	PERCENTAGE(%)
1.Fever	36	76.6
2.Altered sensorium	21	44.7
3.Seizures	14	29.8
4.Decreased urine output	2	4.3
5.Bleeding manifestation	2	4.3
6. Rash	1	2.1

TABLE 2.

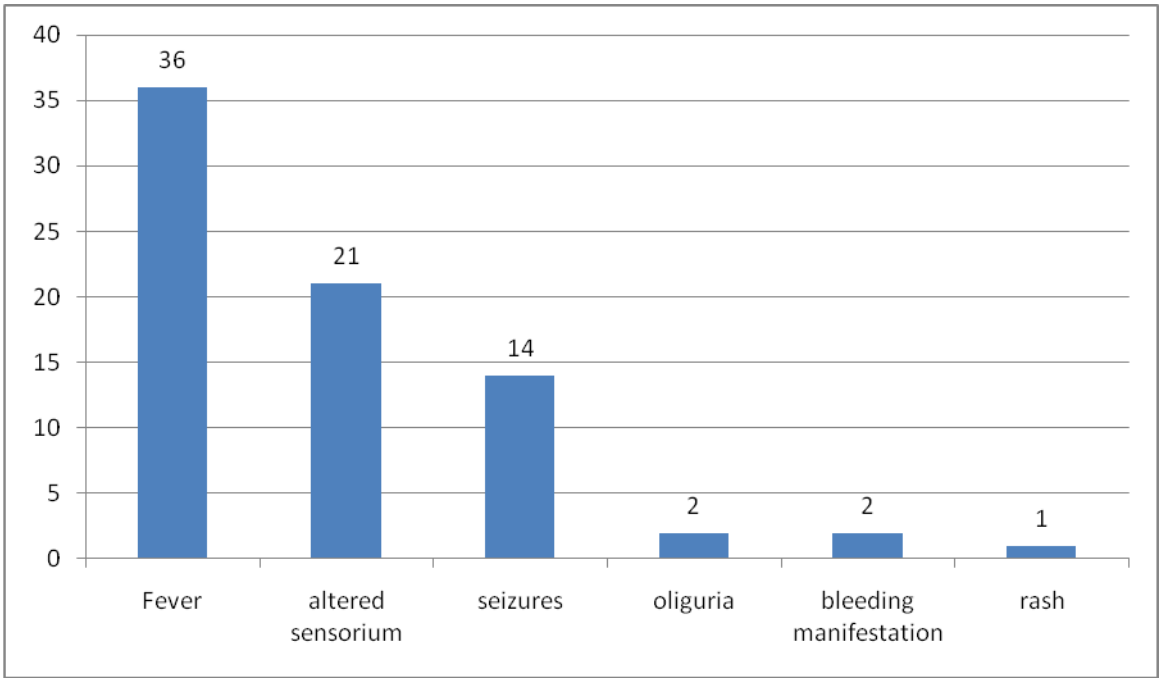


FIGURE 2

Fever was the commonest symptom seen in 36/47 (76.6%) of the children followed by altered sensorium in 21/47 (44.7%) and seizures 14/47 (29.8%).

The others in small numbers included bleeding manifestation 2/47 (4.3%), oliguria 2/47 (4.3%) and rash 1/47 (2.1%).

DURATION OF ILLNESS PRIOR PRESENTATION

DURATION	NUMBER n=47	PERCENTAGE %
1-3 days	**32**	**68**
4-7 days	**13**	**27.7**
>7 days	**2**	**4.3**

TABLE 3.

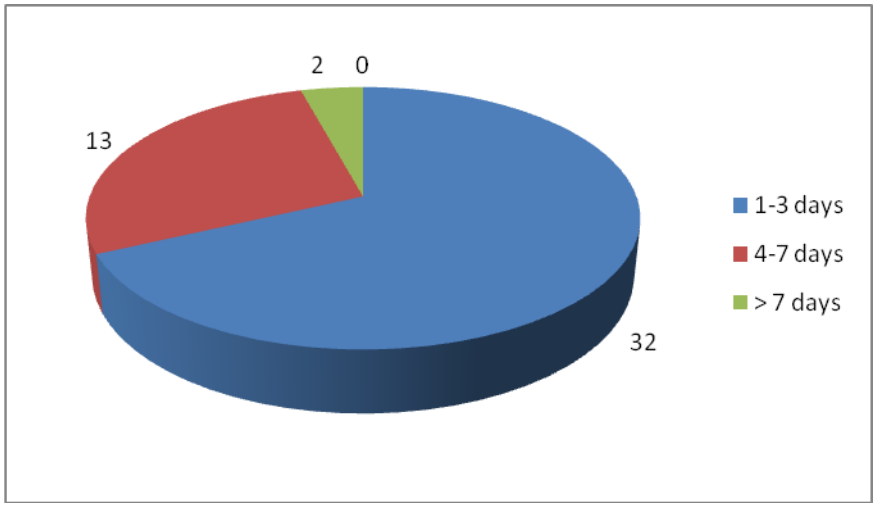


FIGURE 3.

Majority of the children (32/47- 68%) presented within 3 days of onset of illness

The remaining- 13/47(27.7%) presented between 4-7 days.

Only 2/47 (4.3%) presented after being unwell for >7 days (1 week)

DURATION OF HOSPITALISATION PRIOR TO ONSET OF SEPSIS:

DURATION	NUMBER n=47	PERCENTAGE%
None	32	68
1-3 days	14	29.7
>4 days	1	2.1

TABLE 4.

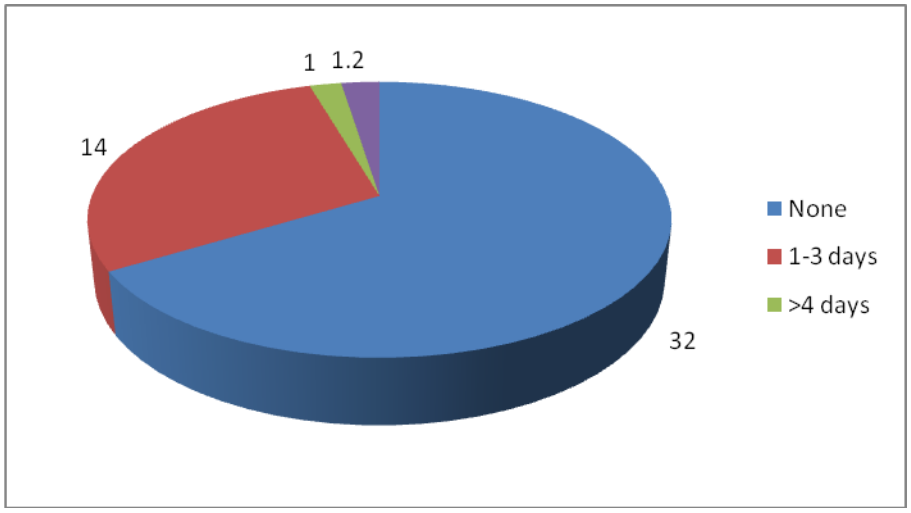


FIGURE 4.

Only 15/47 were hospitalised prior to onset of severe sepsis.

Of these, 14/15 (29.7%) were hospitalised for < 3 days and only 1 (6.6%) child was hospitalised for >4 days.

VITAL SIGNS AT PRESENTATION:

VITAL SIGN	NUMBER n=47	PERCENTAGE %
1.Tachypnoea	34	72.3
2.Hypotension	34	72.3
3.Low GCS	28	59.5
4.Hyper/Hypothermia	24	51.1
5.Tachycardia	21	44.6

TABLE 5.

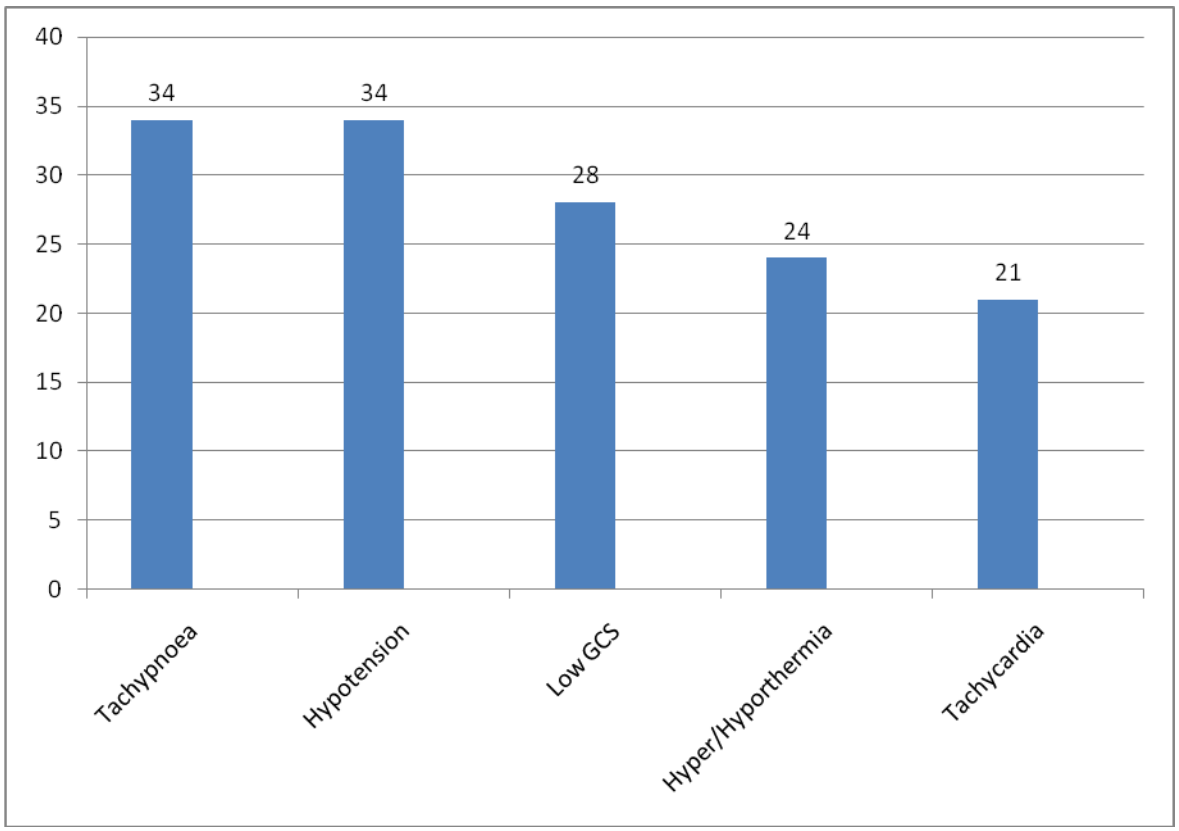


FIGURE 5.

The most common signs at presentation was the presence of tachypnoea and hypotension in 34/47 (72.3%) .

The other common presentations include low GCS in 28/47 (59.5%), temperature instability in 24/47 (51.1%) and tachycardia in 21/47 (44.6%)

INVESTIGATIONS AT PRESENTATION:

INVESTIGATION	NUMBER n=47	PERCENTAGE %
1.Albumin <3.5 g/dl	26	55.3
2.Liver enzymes >250IU/ml	16	34
3.Anaemia	15	31.9
4.Thrombocytopenia	14	29.7
5.PT >22 seconds	8	17
6.APTT > 57 seconds	8	17
7.Hyperbilirubinemia	4	8.5

TABLE 6.

The most common abnormality noted was hypoalbuminemia present in 26/47 (55.3%) of children, followed by deranged liver enzymes in 16/47 (34%), anaemia in 15/47 (31.9%) and thrombocytopenia in 14/47 (29.7%) patients. Coagulopathy was present in 8/47 (17%) and the least common was hyperbilirubinemia seen in 4/47(8.5%).

PELOD SCORE VARIABLES (MODS) IN PICU:

PELOD score assesses the severity of organ dysfunction (MODS) and predicts mortality. It was found to be higher in non-survivors as compared to children who improved and were discharged. The modified PELOD2 score has 10 variables which includes clinical assessment, lab parameters and assessment of each organ involvement.

VARIABLE	NUMBER n=47	%
1.GCS		
<8	**32**	**68**
>15(normal)	**11**	**23.4**
8-15	**4**	**8.5**
2.Pupillary reaction		
Reactive	**43**	**91.4**
Sluggish	**3**	**6.3**
Fixed	**1**	**2.1**
3.Arterial lactate		
1-5	**38**	**80.8**
5-10	**7**	**14.8**
>10	**2**	**4.2**
4.MAP(mmhg)		
35-44	**36**	**76.5**

<35	**7**	**14.9**
>45	**4**	**8.6**
5.Creatinine (mg/dl)		
<0.7	**32**	**68**
0.7-1.2	**11**	**23.4**
>1.2	**4**	**8.5**
6.PaO_2 (mmhg)		
>61	**40**	**85.1**
<60	**7**	**14.8**
7.$Paco_2$ (mmhg)		
>61	**0**	
<60	**47**	**100**
8.Invasive ventilation		
Yes	**36**	**76.6**
No	**11**	**23.4**
9.Total counts(cells/mm^3)		
>2000	**42**	**89.4**
<2000	**5**	**10.6**
10.Platelet count(Lakhs)		
>1.5	**24**	**51.1**
<0.75	**14**	**29.7**
0.75-1.5	**9**	**19.1**

TABLE 7.

PELOD SCORE - LOW GCS:

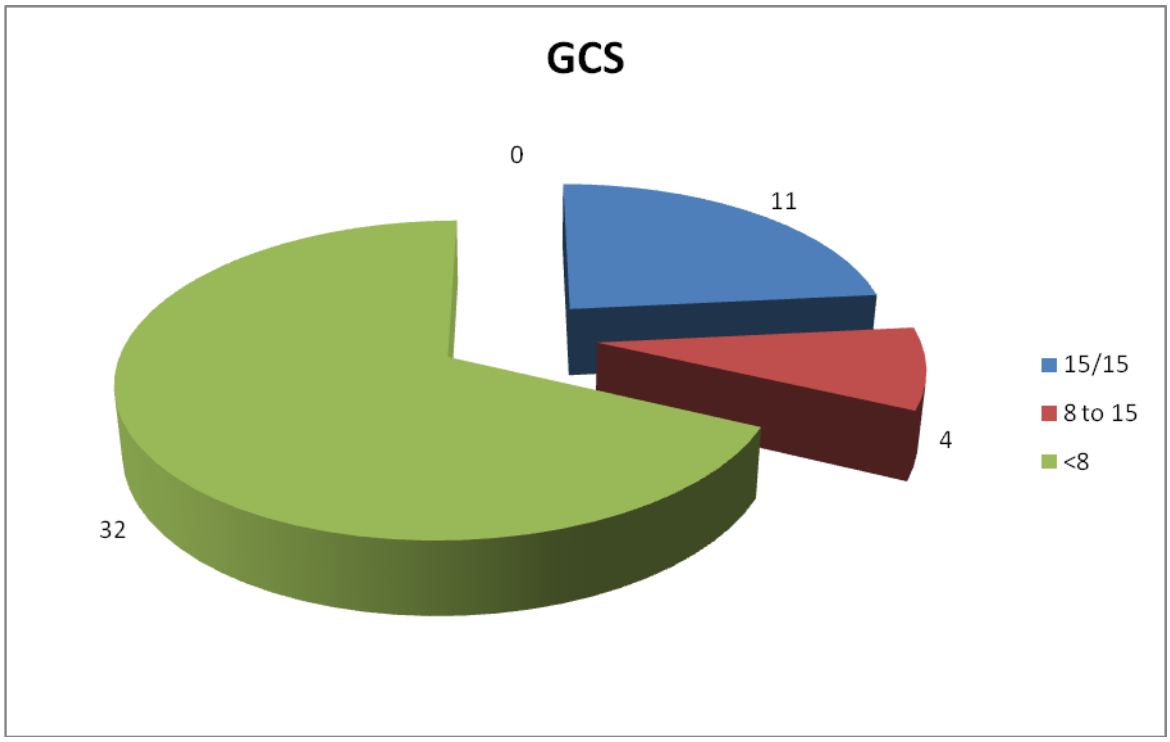


FIGURE 7.1

Of the children with Sepsis, 32/47(68%) had low GCS of <8 and required immediate intubation at admission to PICU while 11/47(23.4%) had a normal GCS.

PELOD SCORE and PUPILLARY REACTION:

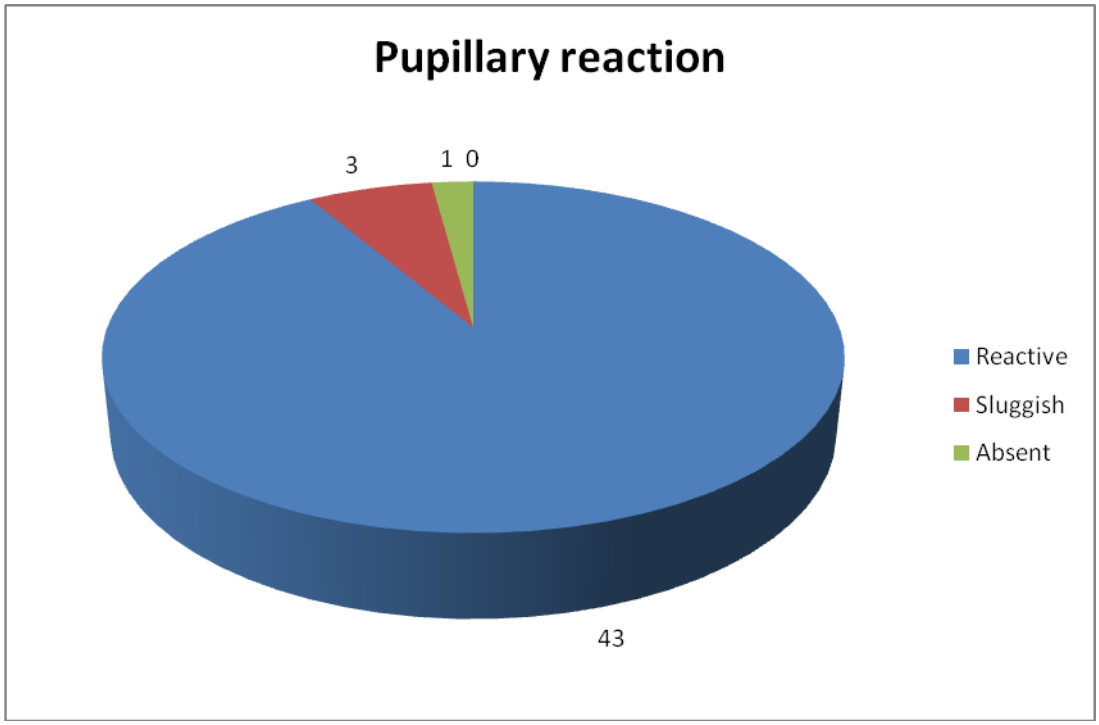


FIGURE 7.2

Most children had normal pupillary reaction -43/47(91.4%)

Of the total- only 3/47 (6.3%) had sluggishly reactive pupils and 1/47(2.1%) had fixed and dilated pupils at admission

PELOD SCORE and ARTERIAL LACTATE

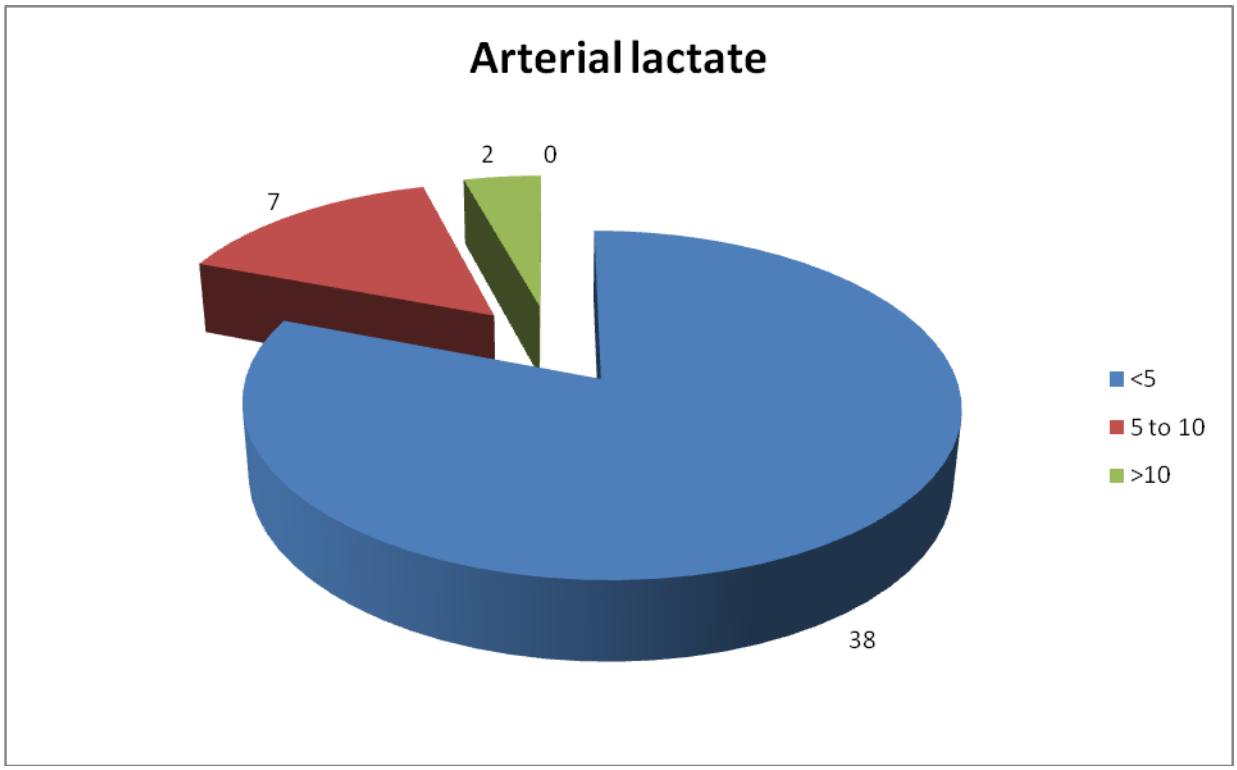


FIGURE 7.3

Arterial lactate of <5 was present in 38/47 (80.8%) of children.

High lactate levels between 5-10 were present in 7(14.8%) and 2/47(4.2%) had> 10

PELOD SCORE AND MAP

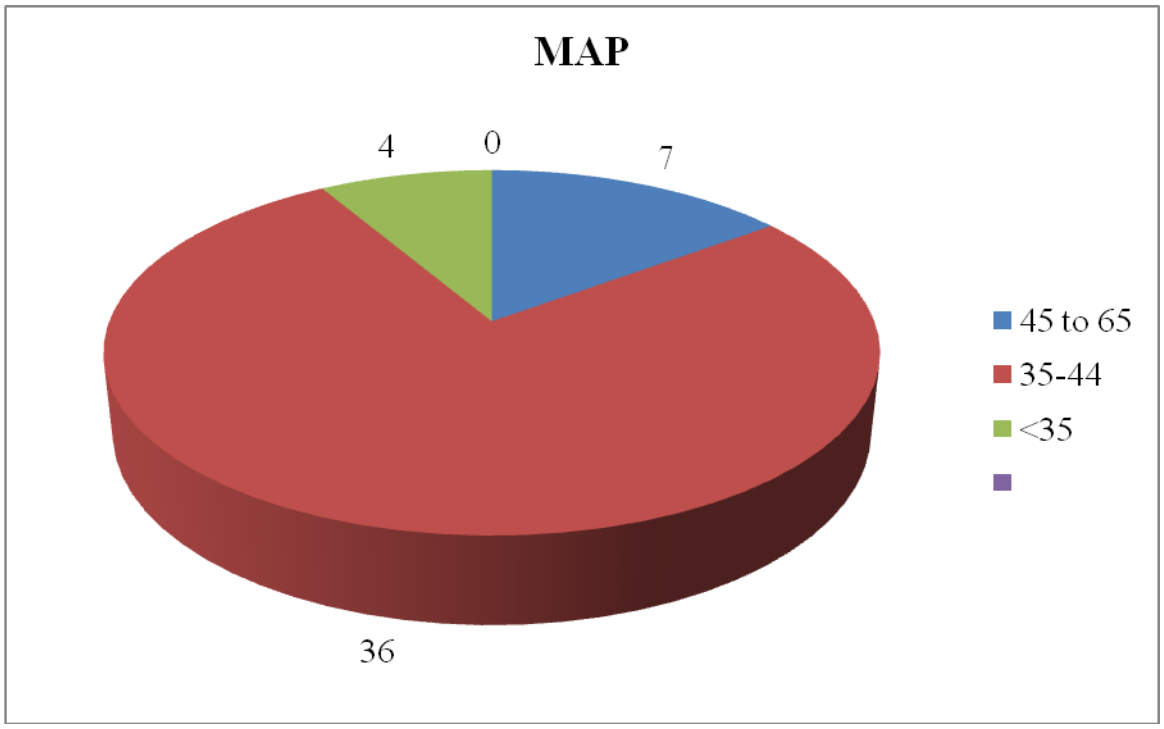


FIGURE 7.4

A very low Mean arterial blood pressure (MAP) of<35mmhg was present only in 4/47(8.6%).

Majority had a MAP between 35-44 mmhg 36/47 (76.5%) followed by MAP of 45-65mmhg in 7/47(14.9%).

PELOD SCORE and SERUM CREATININE

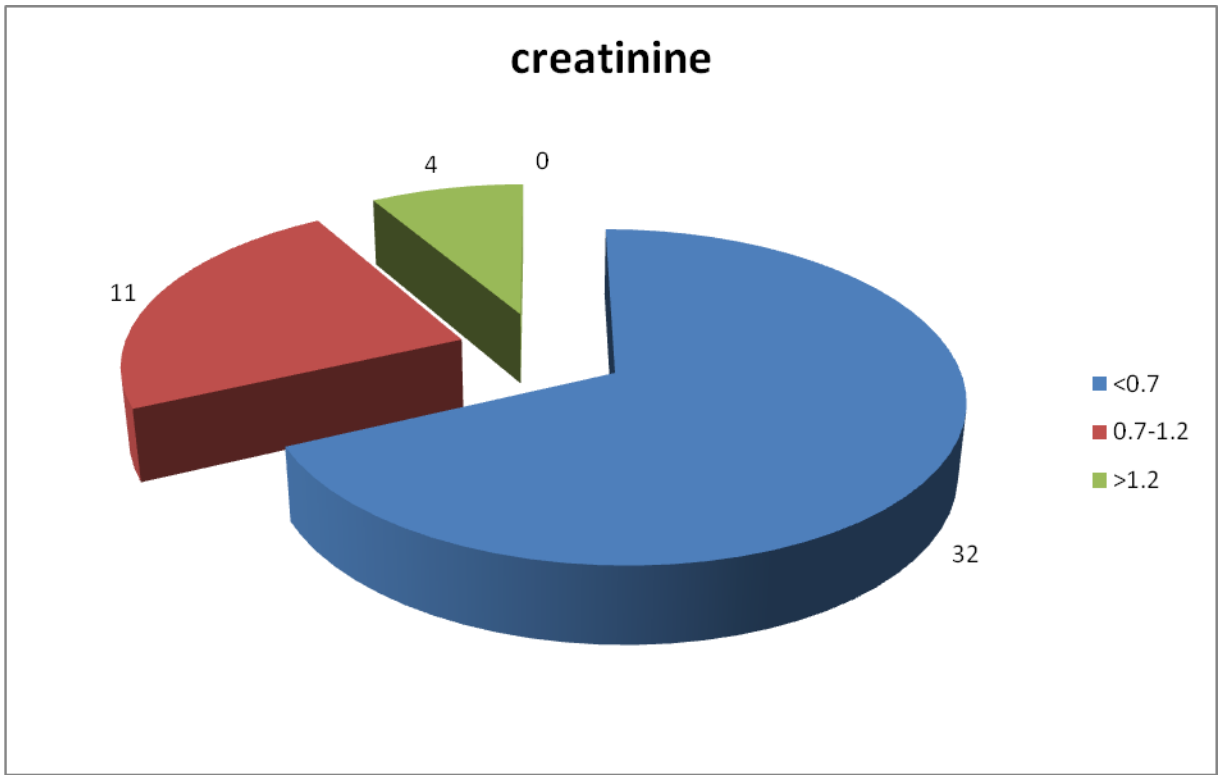


FIGURE 7.5

Serum creatinine was <0.7 in 32 (68%) of children. A higher creatinine in the range 0.7-1.2mg/dl was seen in 11/47(23.4%) while 4/47 (8.5%) had a creatinine value of >1.2mg/dl

PELOD SCORE and PaO2

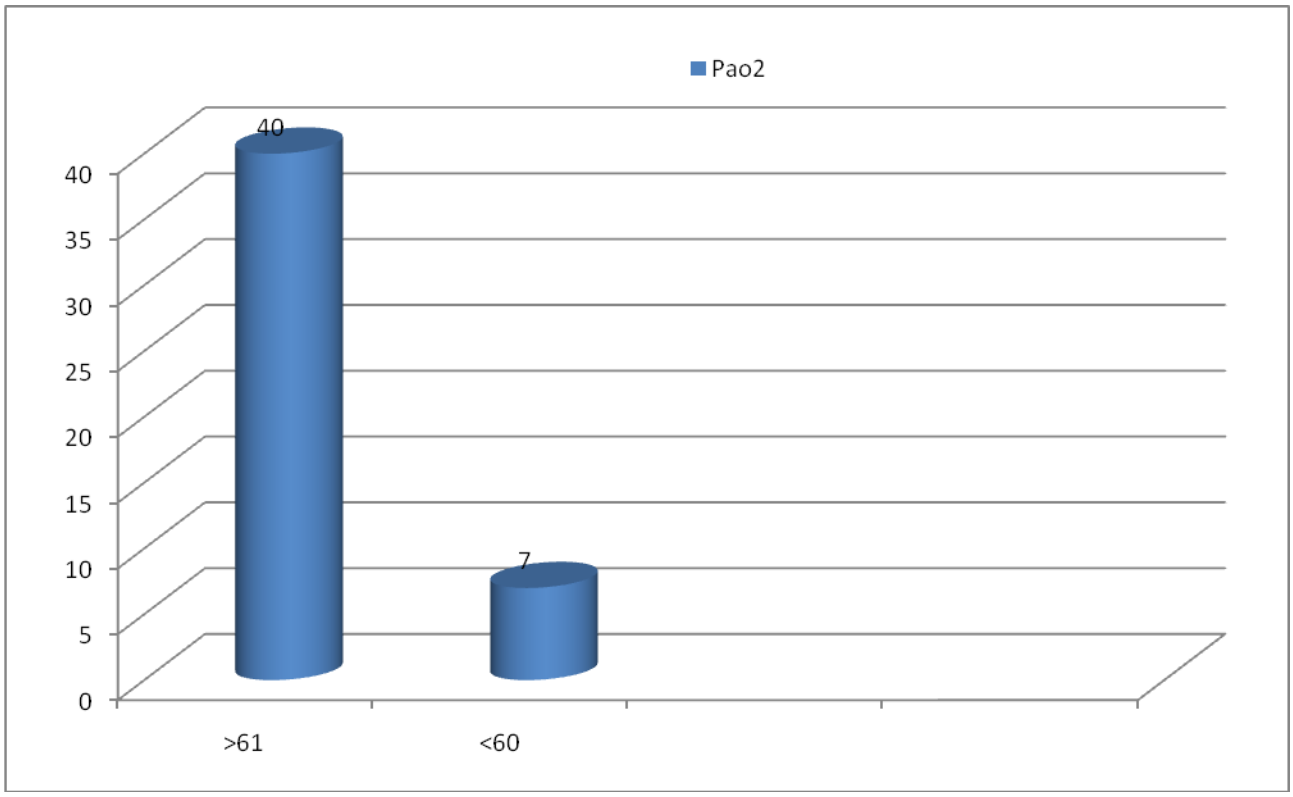


FIGURE 7.6

Majority (40/47- 85.1%) of children had Partial pressure of oxygen ($PaO_{2)}$>61 while PaO_2 was < 60 was present only in 7/47 (14.8%).

PELOD SCORE and INVASIVE VENTILATION

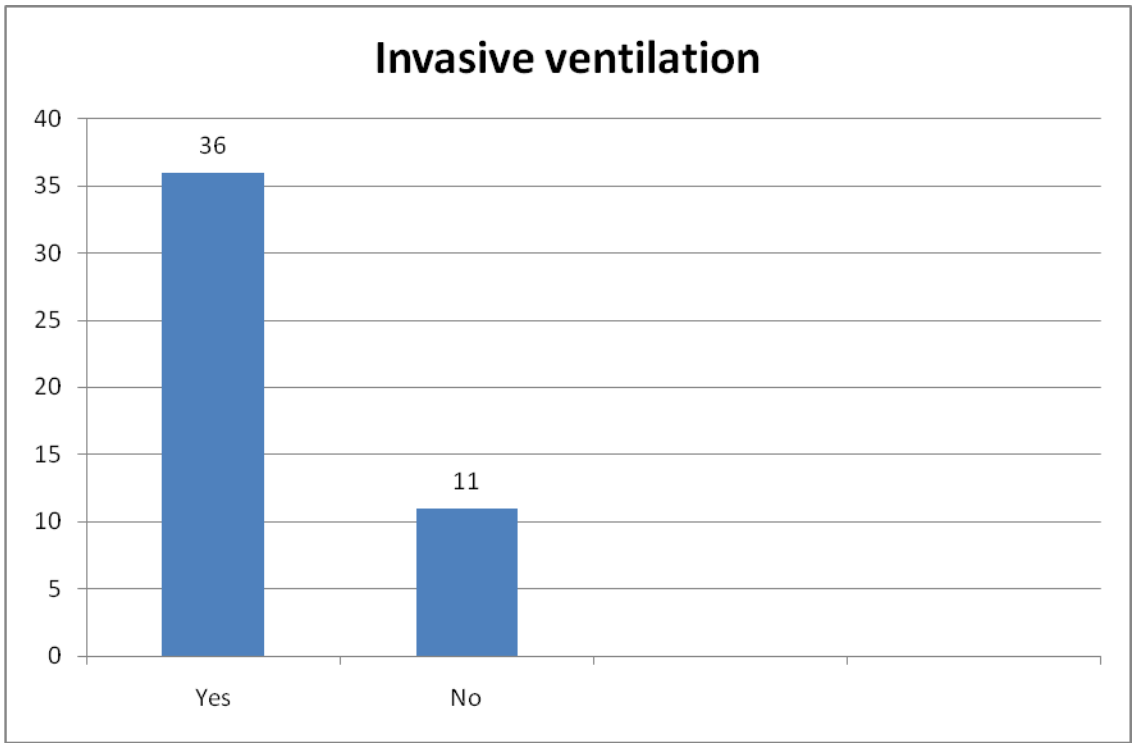


FIGURE 7.7

Of all the children with Sepsis as many as 36/47 (76.6%) of the children required Invasive ventilation.

PELOD SCORE and TOTAL COUNTS:

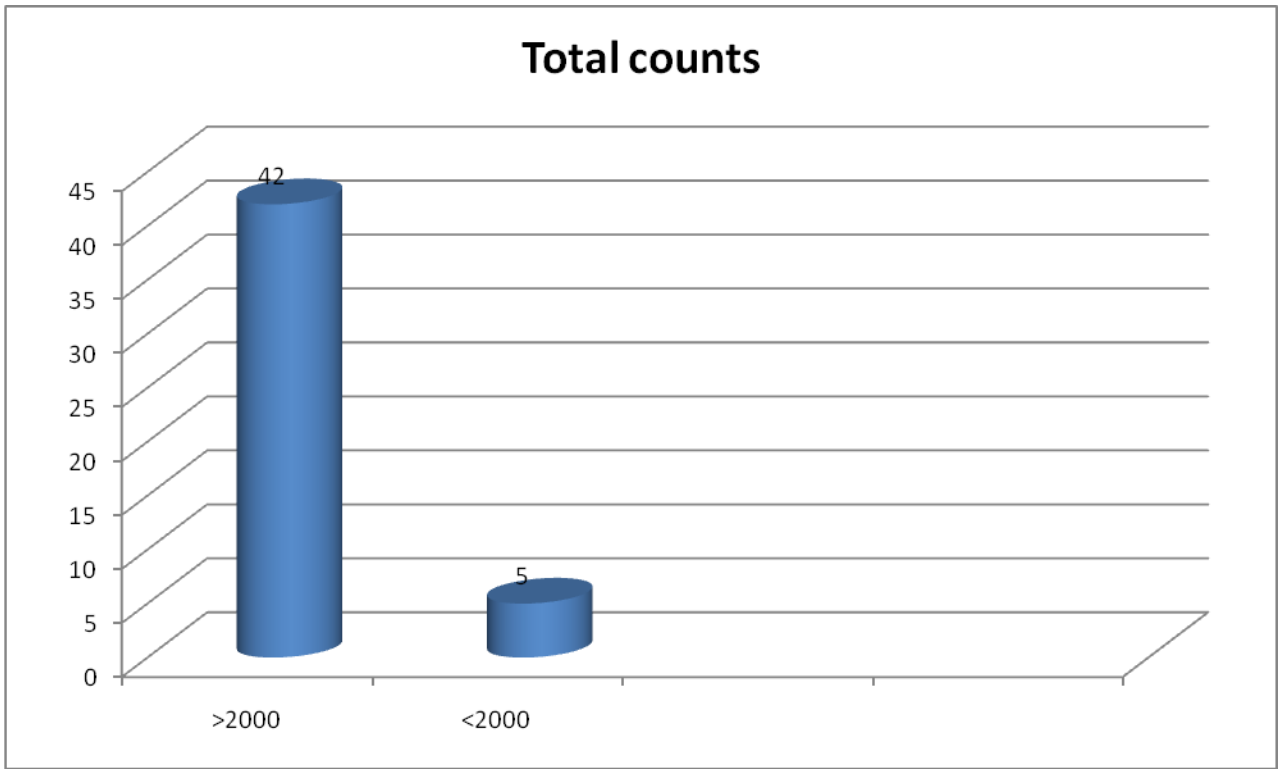


FIGURE 7.8

Total counts was <2000 in only 5/47 (10.6%) of children with sepsis

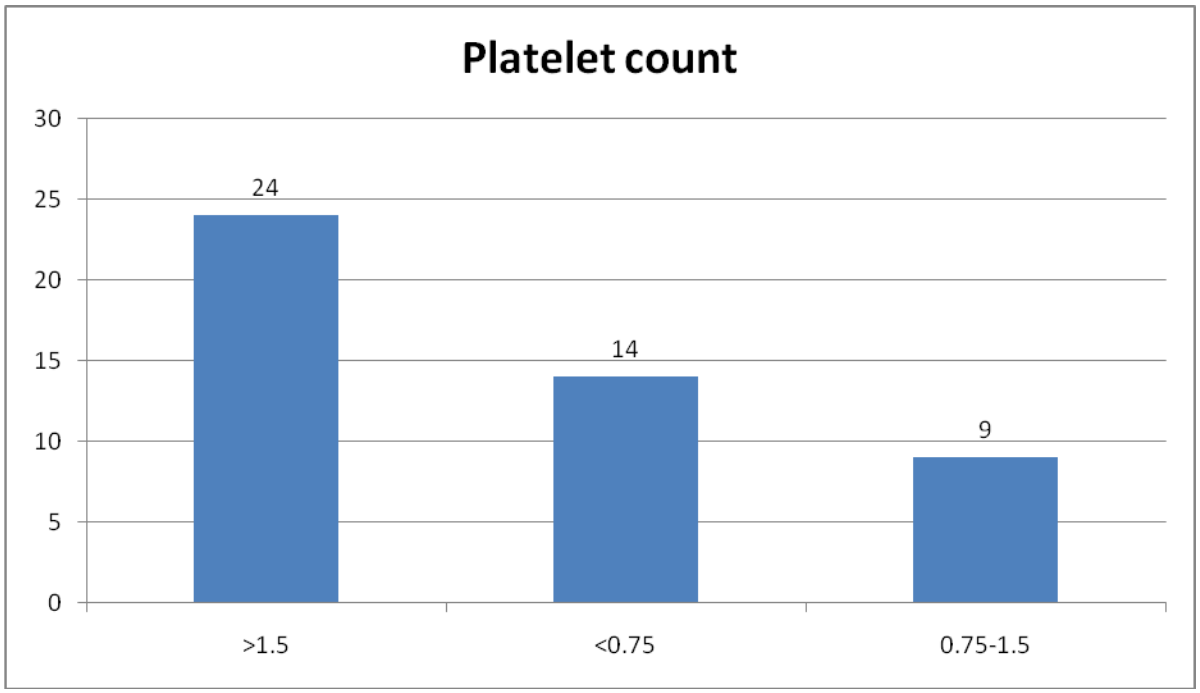


FIGURE 7.9

Thrombocytopenia was present in 23/47 (48.9%) children.

Of these, platelet count of <75,000 was present in 14/23 (60.8%), 9/23 (39.1%) had count between 75,000-1,50,000.

Almost half- 24 47 (51.1%) had a normal platelet count of >1.5 lakhs.

PELOD SCORE:

PELOD SCORE	NUMBER(n=47) AT ADMISSION	NUMBER (n=47) AT 48 hrs
<10(n=15)	15/47(31.9%)	18/47(38%)
10-20(n=26)	26/47(55.3%)	12/47(25.5%)
>20(n=6)	6/47(12.7%)	12(25.5)

TABLE 8.

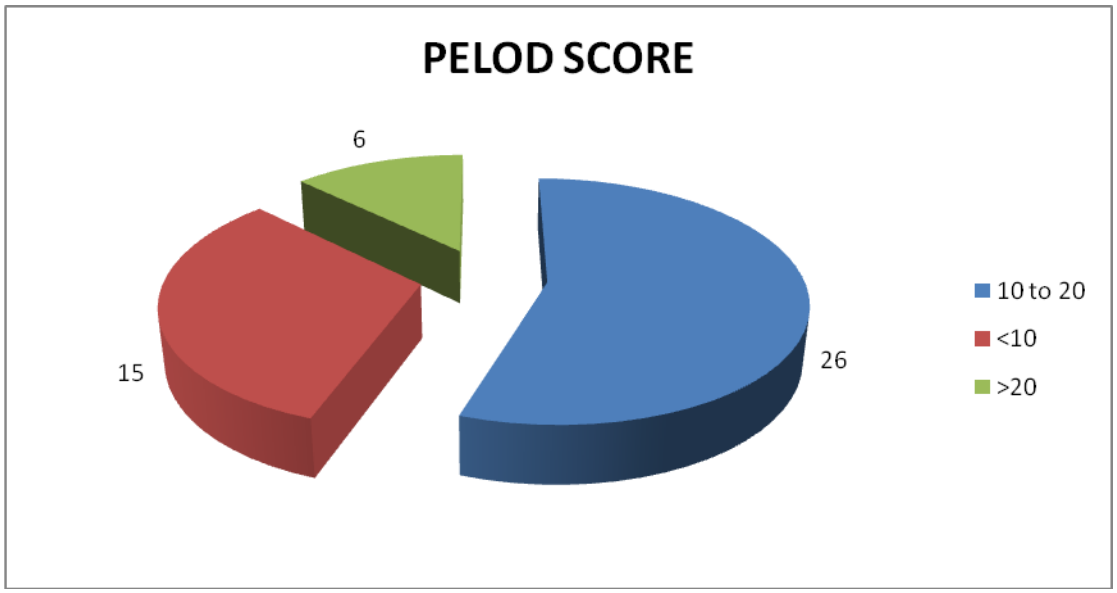


FIGURE 8:

PELOD score was high in non-survivors as compared to survivors

A score of >20 was present in 6 patients and mortality was 100% in them

Score of 10-20 was present in 26, mortality in this group was 61.5% (16/26).

REQUIREMENT OF INOTROPIC SUPPORT:

INOTROPIC SUPPORT	NUMBER n=47	PERCENTAGE%
<72 hours	**30**	**63.8**
>72 hours	**17**	**36.1**

TABLE 9

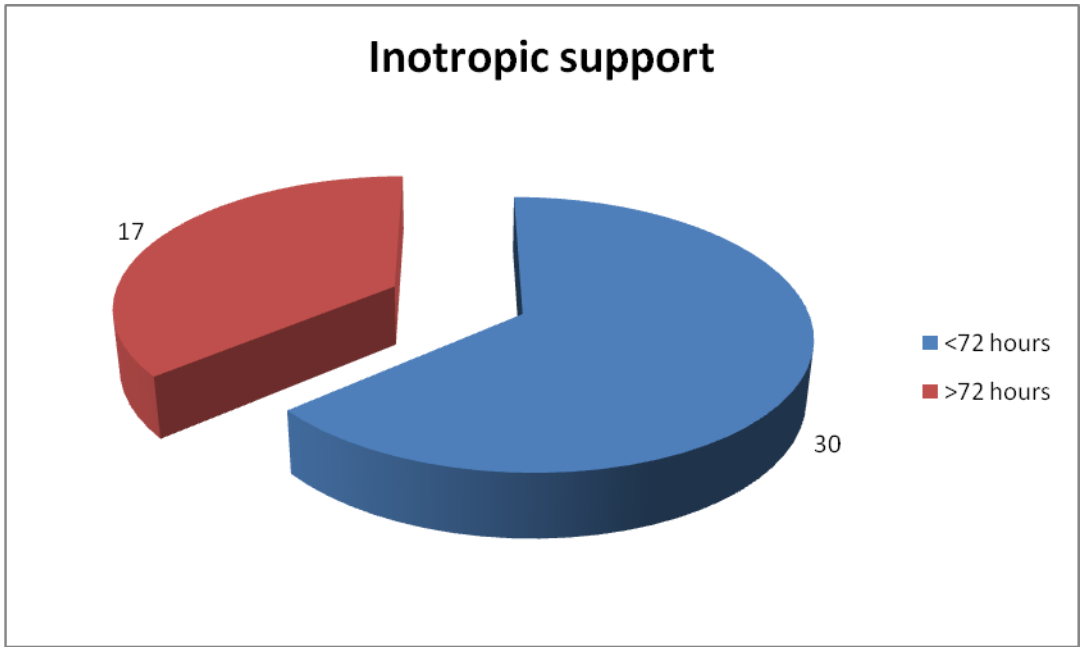


FIGURE 9.

All 47 children needed inotropic support to maintain a normal blood pressure

Of these, almost one thirds-17/47 (36.1%) needed inotropic support for >72 hours

Two thirds -30/47 (63.8%) needed inotropic support for <72 hours.

REQUIREMENT OF BLOOD PRODUCTS:

BLOOD PRODUCTS	NUMBER n=47	PERCENTAGE%
Yes	**27**	**57.4**
No	**20**	**42.5**

TABLE 10.

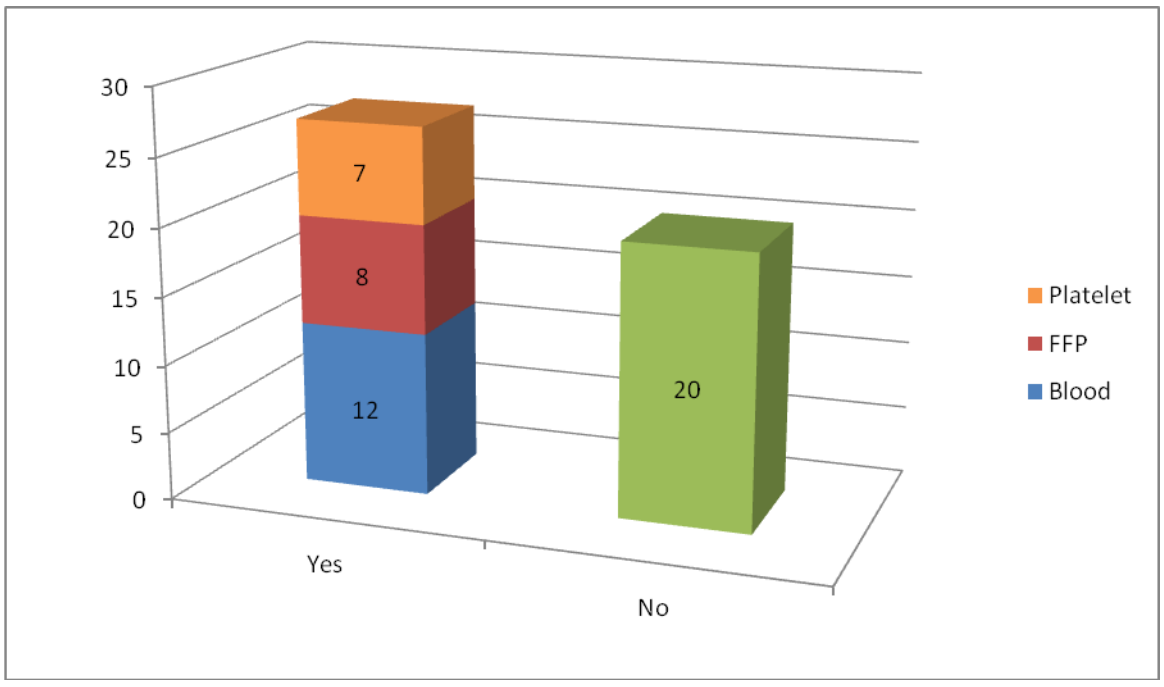


FIGURE 10.

Of the total, 27/47 (57.4%) of the children required transfusion of various blood products

DURATION OF INVASIVE VENTILATION:

INVASIVE VENTILATION	NUMBER n=38	PERCENTAGE%
<72 hours	**22**	**57.8**
>72 hours	**16**	**42.1**

TABLE 10.

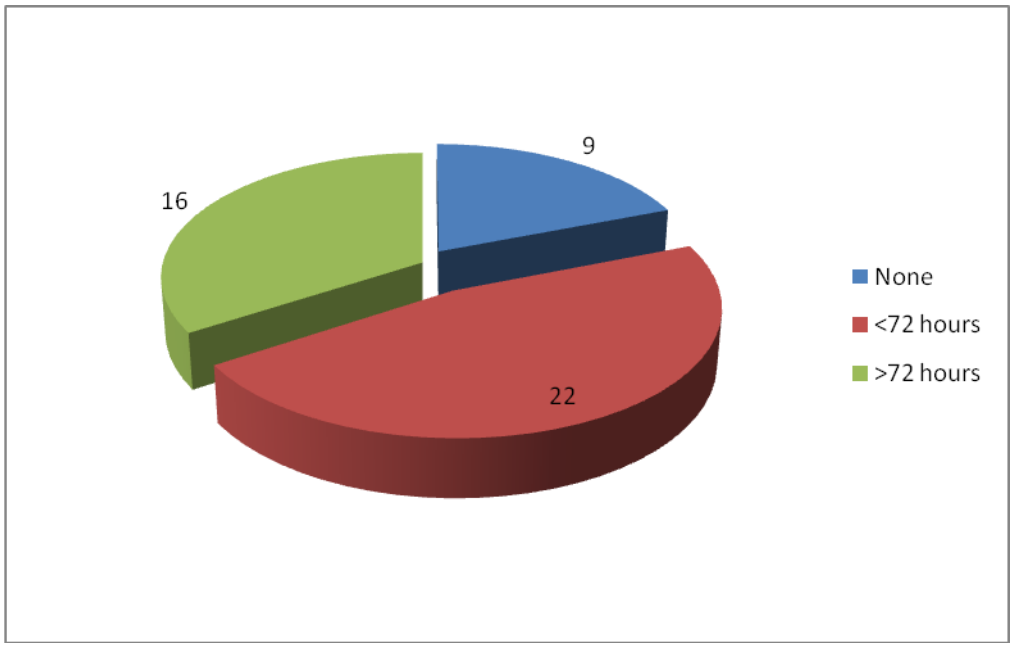


FIGURE 10.

42.1%(16/38) required invasive ventilation for >72hrs,

57.8%(22/47) required invasive ventilation for only <72hrs.

SITES OF CULTURE:

PRIMARY SEPSIS:

	NUMBER(n=47)	PERCENTAGE (%)
Blood culture positivity	**13**	**27.6**
BAL positivity	**8**	**17**

TABLE 11.

SECONDARY SEPSIS:

	NUMBER	PERCENTAGE (%)
Post-op	**4**	**8.5**
Burns	**2**	**4.2**
Central associated blood stream infection(CLABSI)	**1**	**2.1**

TABLE 12.

Out of the 47 children with severe sepsis 40/47(85.1%) had primary sepsis, 7/47(14.8% %) had secondary sepsis. Blood culture was positive only in 13/47 (27.6%) patients.

Of the 14.8%(7/47) patients with secondary sepsis, 4 were post-operative patients, 2 had burn injury and 1 was central line associated blood stream infection.(CLABSI).

The commonest organism was Pseudomonas which was carbapenemase resistant organisms (CRO) in 3/13(23%), while 2/13(15.3%) each had MRSA (methicillin resistant staphylococcus aureus) and Non-fermenting gram negative bacilli(CRO) the species of which was not identified and Candida tropicalis.

The remaining organisms included 1/13 (7.6%) each of Hemophilus influenza, Enterococcus, Klebsiella.

Bronchoalveolar lavage was positive in 8/47 (17 %).

These included 2 growths of Candida tropicalis and 1 each of MRSA, alpha hemolytic streptococcus, pseudomonas (CRO).

ACUTE KIDNEY INJURY:

The study population of Severe sepsis were assessed for the presence of AKI

The **AKIN Criteria** was used to diagnose AKI.

The first creatinine value at admission was considered the baseline. All patients included in our study were catherised and urine output was monitored every hour. Creatinine levels were done everyday thereafter.

The creatinine clearance was calculated as per the Modified Swartz formula.

A Urine sample was also collected for our study biomarker at admission and 48 hours later.

INCIDENCE OF ACUTE KIDNEY INJURY:

AKI	NUMBER(n=47)
NORMAL	22(46.8%)
STAGE 1	15(31.9%)
STAGE 2	4(8.5%)
STAGE 3	6 (12.7%)

TABLE 12.

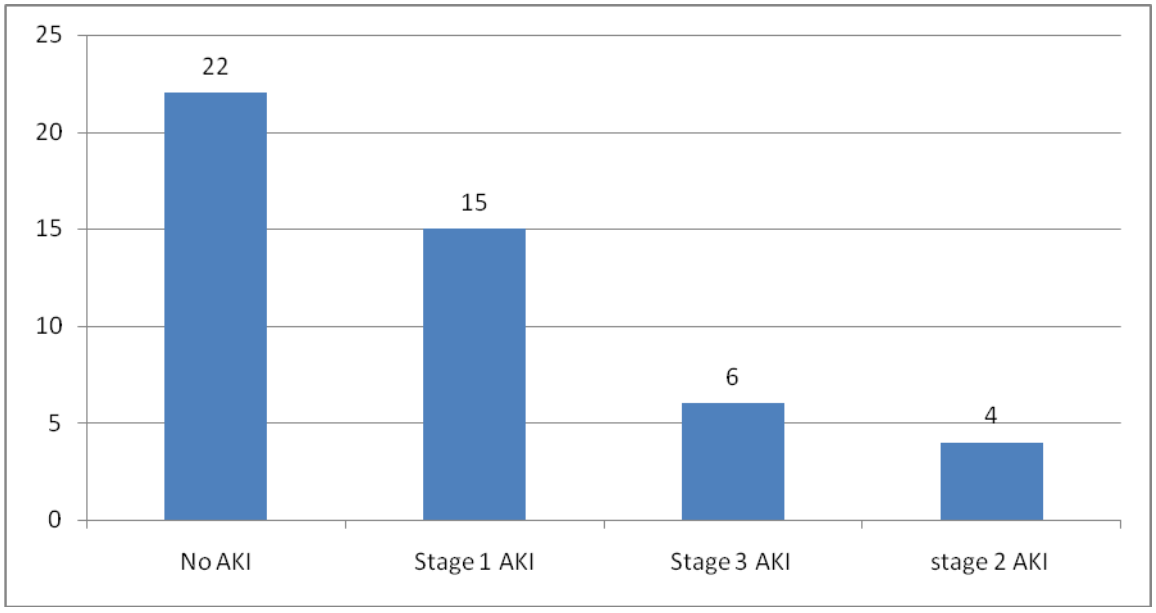


FIGURE 11.

Amongst children with Severe sepsis 53.1% (25/47) were diagnosed to have AKI.

Of these 60%(15/25) were in stage 1, 16%(4/25) were in stage 2 and 24% (6/25) were in stage 3

DEMOGRAPHIC CHARACTERS AND AKI :

n=47	**No AKI (n=22)**	**Stage1 (n=15)**	**Stage 2 (n=4)**	**Stage 3 (n=6)**
Age				
<1 year (n=5)	**5**	**1**	**0**	**0**
1-5 years(n=23)	**9**	**10**	**0**	**4**
>5 years(n= 18)	**8**	**4**	**4**	**2**
Sex				
Male(n=23)	**11**	**8**	**1**	**3**
Female(n=23)	**11**	**7**	**3**	**3**
Normal Nutrition				

(n= 24)	**9**	**10**	**1**	**4**
Moderate malnutrition (n=10)	**8**	**0**	**1**	**1**
Severe malnutritio(n=13)	**5**	**5**	**2**	**1**

TABLE 13.

Majority of children with AKI were between 1-5 years of age

M:F ratio was 1:1

Severe malnutrition was present in 13/45 (28.8 %).

Of these, 8/13 (61.5%) had AKI.

RISK FACTORS OF AKI:

SYMPTOMS	NO AKI (n = 22)	AKI (n = 25)
1.Fever (n=36)	14/36(38%)	**22/36(61%)** **22/25(88%)**
2.Bleeding manifestation (n=2)	1/2(50%)	1/2(50%) 1/25 (4%)
3.Oliguria (n=2)	**0**	2/2(100%) **2/25(8%)**
4.Seizures (n=14)	6/14(42%)	8/14(57%) 8/25(32%)
5.Low GCS (n=21)	9/21(42%)	12/21(57%) **12/25(48%)**
VITAL SIGNS: **1**.Tachycardia (n=36)	14/36(38%)	**22/36(61%)** **22/25 (88.8%)**

2.Tachypnea (n=21)	7/21(33.3%)	**14/21(66.7%)** **14/25 (56%)**

TABLE 14.

	NO AKI (n = 22)	AKI (n = 25)
3.Hypotension (n=34)	**15/22(68%)** **15/34(44%)**	**19/25(76%)** **19/34(55%)**
LAB PARAMETERS : **1**.Anaemia (n=15)	**9/15(60%)** 9/22(40%)	**6/15(40%)** 6/25(24%)
2.Thrombocytopenia (n=14)	6/14(42%) 6/22(27%)	8/14(57%) 8/25(32%)
3.Hyperbilirubinemia (n=7)	4/7(57%) 4/22(18%)	3/7(42%) 3/25(12%)
4.Elevated liver enzymes(n=7)	4/7(57%) 4/22(18%)	3/7(42%) 3/25(12%)
5.Coagulopathy (n=8)	**3/8(37%)** **3/22(13%)**	**5/8(62%)** **5/25(20%)**

INTERVENTION: **1.Ventilation >72hrs (n=16)**	6/16(37%) **6/22(27%**)	**10/16(62%)** **10/25(40%)**
2.Duration of inotropes >72hrs(n=17)	5/17(29%) **5/22(22%)**	**12/17(70%)** **12/25(48%)**

Cont..TABLE 14.

Among the children with AKI 88% had fever, 56% had tachypnoea, 48% had low GCS and only 8% had oliguria.

When the AKI and non-AKI group were compared we found that in the AKI group 88% had tachycardia, 76% had hypotension and 56% had tachypnoea. However amongst those who had hypotension there was no difference seen between AKI and non-AKI group.

Amongst those who required prolonged ventilation and prolonged duration of inotropic support the risk of AKI was higher (40% Vs 27%) and (48% Vs 22%) respectively.

RISK FACTORS FOR AKI – SYMPTOMS:

	NORMAL	AKI	ODDS RATIO	P value
Age >1 year(n=41)	17/39(43%)	24/39(61%)	7.059 0.755-65.983	0.087
Fever(n=36)	14/36(38.9%)	22/36(61.1%)	4.190 0.948-18.529	0.059
Oliguria(n=2)	**0**	**2/2(100%)**	**1.957** **1.470-2.604**	**0.043**
Seizures(n=14)	6/14(42.9%)	8/14(57.1%)	1.255 0.356-4.422	0.724
Altered sensorium(n=21)	9/21(42.9%)	12/21(57.1%)	1.33 0.419-4.239	0.626
Bleeding manifestation(n=2)	1/2(50%)	1/2(50%)	0.875 0.051-14.872	0.926

TABLE 15.

Oliguria was the only symptom which significantly increased the risk for AKI

(OR: 1.957; 95% CI :1.470-2.604, p value <0.043).

RISK FACTORS FOR AKI –SIGNS:

	NORMAL	AKI	ODDS RATIO	P value
Tachycardia(n=36)	14/36(38.9%)	22/36(61.1%)	4.190 0.948-18.529	0.059
Tachypnoea (n=21)	7/21(33.3%)	14/21(66.7%)	2.727 0.825-9.011	0.100
Hypotension(n=34)	15/34(44%)	19/34(55%)	1.816 0.274-12.014	0.536
Anaemia (n=15)	9/15(60%)	6/15(40%)	0.456 0.131-1.594	0.219
Thrombocytopenia (n=14)	6/14(42%)	8/14(57%)	1.255 0.356-4.422	0.724

Cont..TABLE 15.

None of the clinical findings on examination significantly increased the risk for AKI

RISK FACTORS FOR AKI –LAB FINDINGS

	NORMAL	AKI	ODDS RATIO	P value
Hyperbilirubinemia (n=7)	4/7(57%)	3/7(42%)	0.500 0.370-0.677	0.556
Elevated liver enzymes(n=7)	4/7(57%)	3/7(42%)	0.648 0.150-2.794	0.662
Coagulopathy (n=8)	3/8(37%)	5/8(62%)	0.711 0.162-3.115	0.651
Ventilation >72hrs (n=16)	6/16(37%)	10/17(62%)	1.816 0.474-12.414	0.351
Duration of inotropes>72hrs(n=17)	5/17(29%)	12/17(70%)	2.400 0.202-28.451	0.488

Cont..TABLE 15.

None of the clinical findings on Lab evaluation significantly increased the risk for AKI

OUTCOME OF SEVERE SEPSIS:

OUTCOME	NUMBER(n=47)
DISCHARGED(n=23)	23/47 (48.9%)
DIED(n=16)	16 /47 (34%)
DISCHARGED AGAINST MEDICAL ADVISE(DAMA)(n=8)	8/47 (17%)

TABLE 16.

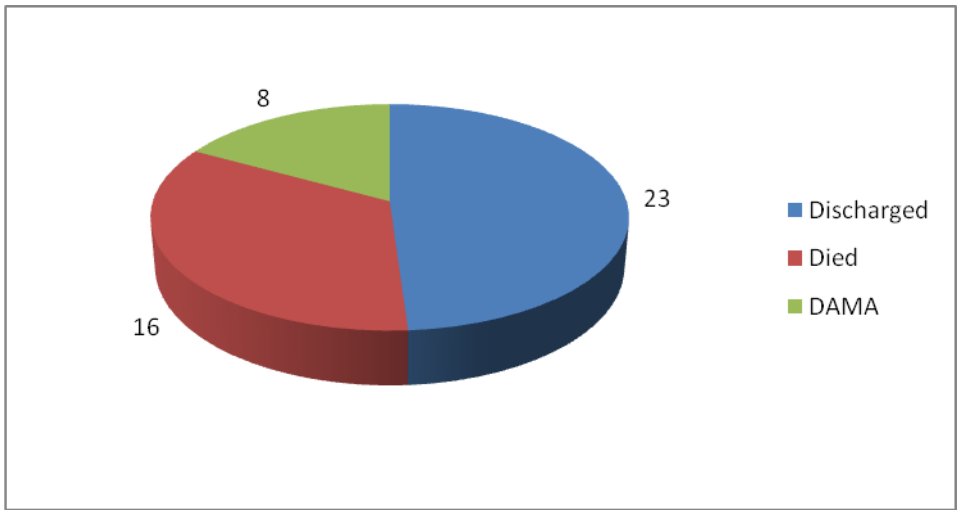


FIGURE 16.

23/47(48.9%) were discharged

16/47(34%) died, 8/47(17%) were discharged against medical advice. Children who died and DAMA were analysed together as poor outcome group 24/47(51.1%).

COMPARISON OF OUTCOME WITH AKI:

	Discharged (n=23)	Died/DAMA (n=24)
No AKI(n=22)	15/22(68.1%)	7/22 (31.85) **7/24 (29.2%)**
Stage 1(n=15)	8/15(53.3%)	7 /15 (46.6%) **7/24 (29.2%)**
Stage 2(n=4)	1/4(25%)	3/4 (75%) **3/24(12.5%)**
Stage 3(n=6)	0	6/100 (100%) **6/24 (25%)**

TABLE 17.

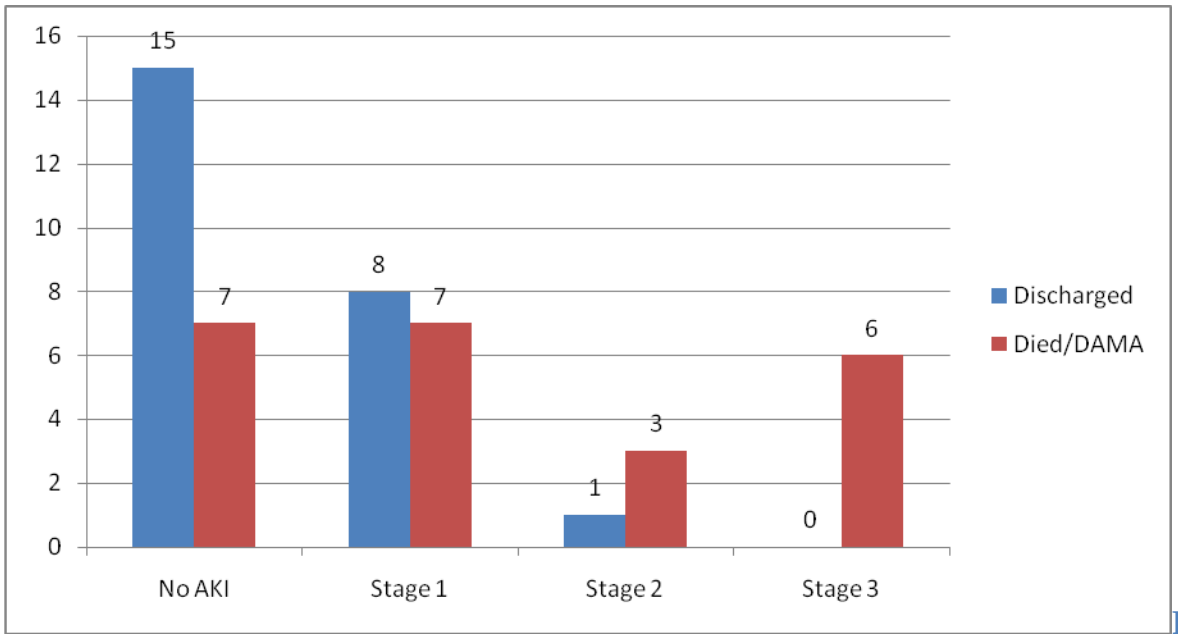


FIGURE 17.

The overall mortality amongst children with AKI was 66.7% (16/23)

There was no difference in the mortality between the different stages of AKI .

ANALYSIS OF STUDY BIOMARKER - L-FABP :

There were 49 patients who fulfilled the inclusion criteria for severe sepsis and were catherised for monitoring urine output.

However 2 patients died within a few hours of admission hence they were excluded from study.

Of the 47 samples collected, the ELISA for L FABP was run on 40 samples.

These results were subjected to further analysis.

L-FABP AT BASELINE:

RANGE OF L-FABP VALUES AT BASELINE:

RANGE(ng/dl)	NUMBER(n=40)	PERCENTAGE %
0-50	20	50%
50-150	9	22.5%
150-500	11	27.5%

TABLE 19.

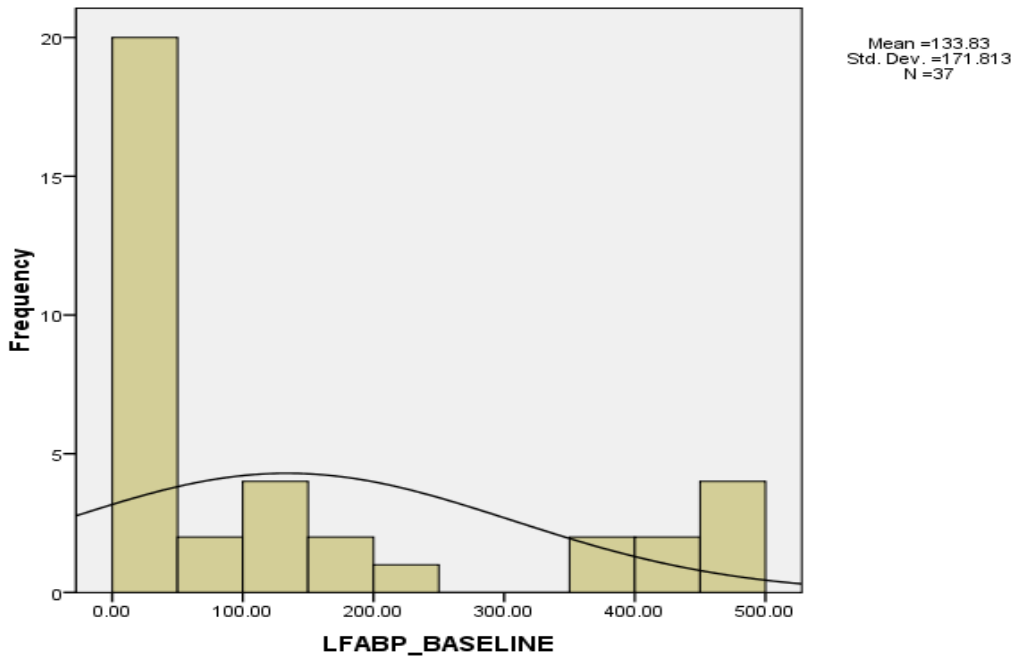


FIGURE 18.

L-FABP AT 48 hrs:

RANGE(ng/dl)	NUMBER(n=40)	PERCENTAGE %
0-50	25	62.5%
50-150	7	17.5%
150-500	8	20%

TABLE 20.

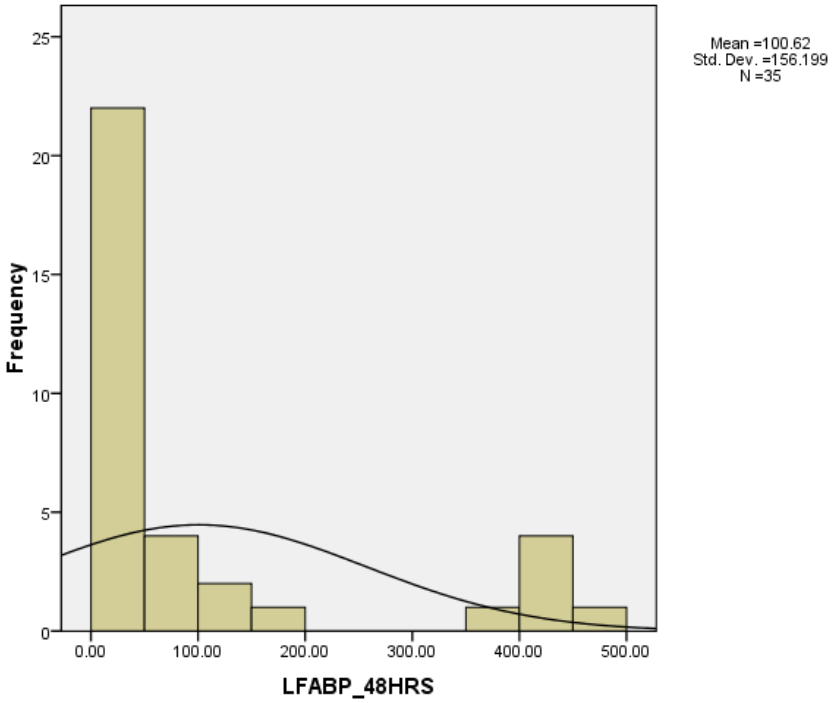


FIGURE 19.

L-FABP: AKI Vs NON-AKI

	AKI GROUP	NON-AKI GROUP	P VALUE
L-FABP AT BASELINE MEDIAN (IQR)	39.42 (7.64 - 190.35)	28.61 (8.04-380.88)	0.778
L-FABP AT 48 hrs MEDIAN (IQR)	24.05 (4.56 – 114.05)	14.61 (10.26- 101.61)	0.946

TABLE 21.

Median L-FABP level at baseline was 1.3 times more in the AKI group compared to the Non-AKI group. However this was not statistically significant (p = 0.778)

The change of L-FABP levels from at baseline to 48hrs also could not predict AKI (p=0.946)

L-FABP: SURVIVORS Vs NON-SURVIVORS:

	NON-SURVIVORS	SURVIVORS	P VALUE
L-FABP AT BASELINE **MEDIAN (IQR)**	**119.08 (11.50 - 412.76)**	21.87 (4.05 – 101.24)	**0.048**
L-FABP AT 48 hrs **MEDIAN (IQR)**	**22.06 (7.90 - 154.17)**	17.95 (4.79 – 98.37)	0.667

TABLE 22.

At admission, L-FABP level was able to differentiate survivors and non-survivors with a p value of 0.048.

However at 48 hours there was no difference in L-FABP levels between the survivors and non-survivors (p=0.667).

COMPARISON OF L-FABP WITH PELOD SCORE

	PELOD >10(n=23)	PELOD <10(n=24)	P VALUE
L-FABP AT BASELINE **MEAN ±(SD)**	3.96 (2.46)	3.59 (2.04)	0.070
L-FABP AT 48 hrs **MEAN ± (SD)**	2.63 (2.46)	3.45 (2.18)	0.103

TABLE 23.

L-FABP was compared with PELOD score for assessing multi-organ dysfunction and mortality

Mean L-FABP levels compared against PELOD score of >10 could predict multi-organ dysfunction (MODS) and mortality. However it was not statistically significant (p = 0.07).

L-FABP Vs AKI: ROC CURVE

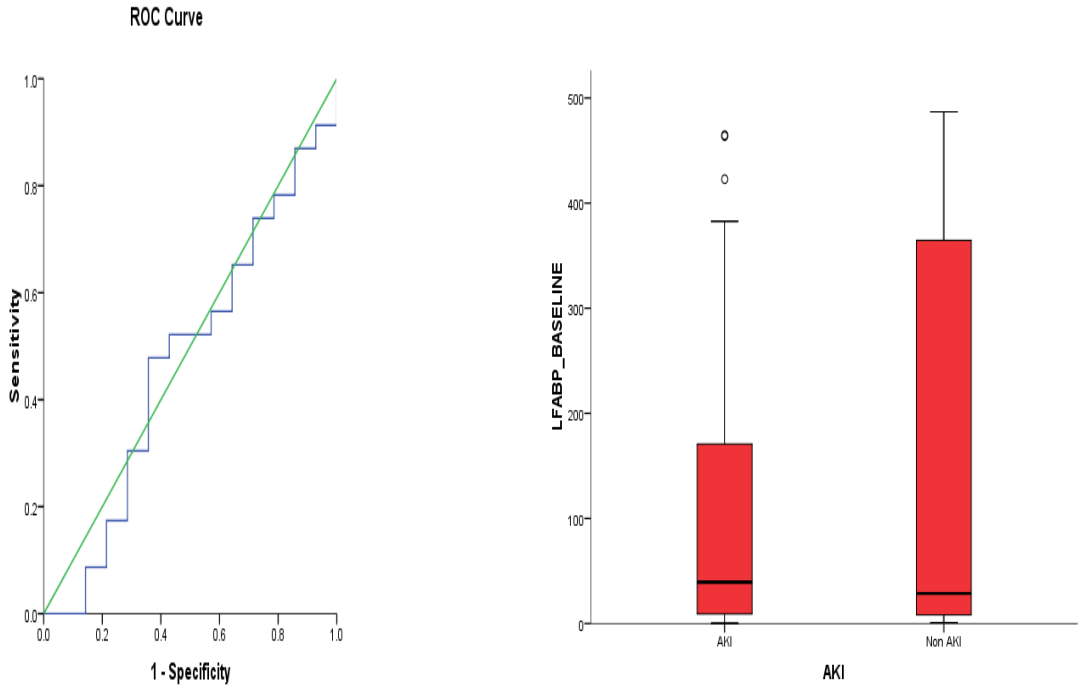


FIGURE 20.

The sensitivity and specificity of L-FABP in diagnosing AKI was 26.1% and 71.4% respectively

L-FABP WITH MORTALITY

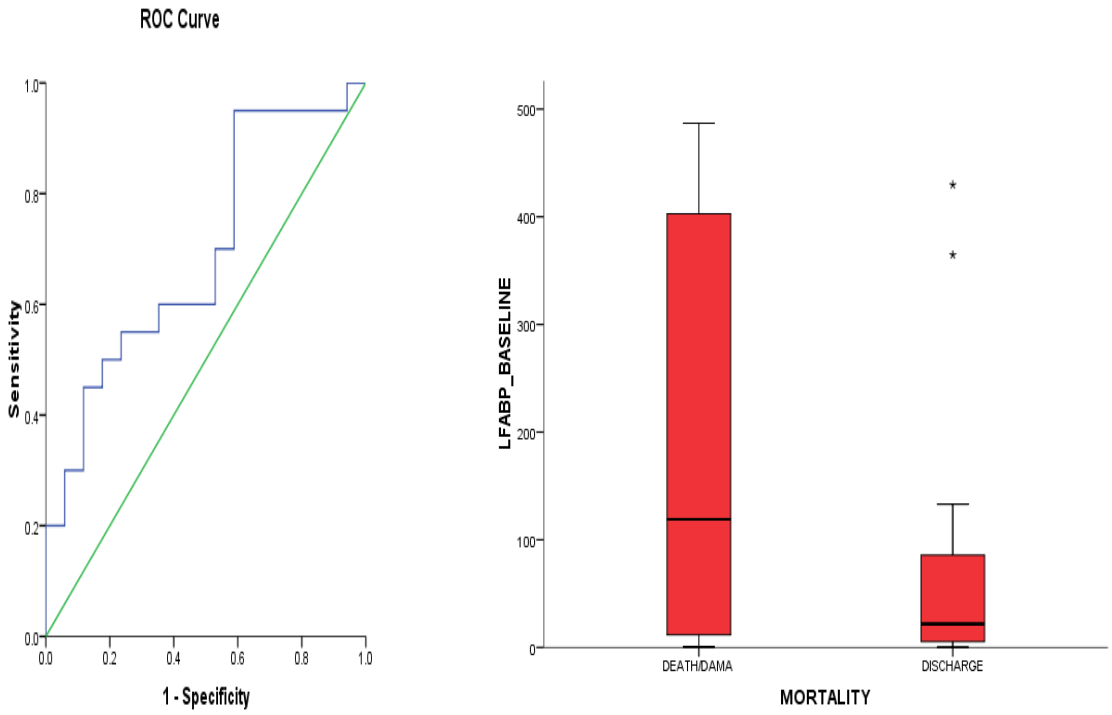


FIGURE 21.

L-FABP on admission was found to be a good predictor of mortality with a sensitivity of 40% and specificity of 88.2%

L-FABP baseline AUC- 0.6910, p value 0.048

PELOD Vs MORTALITY

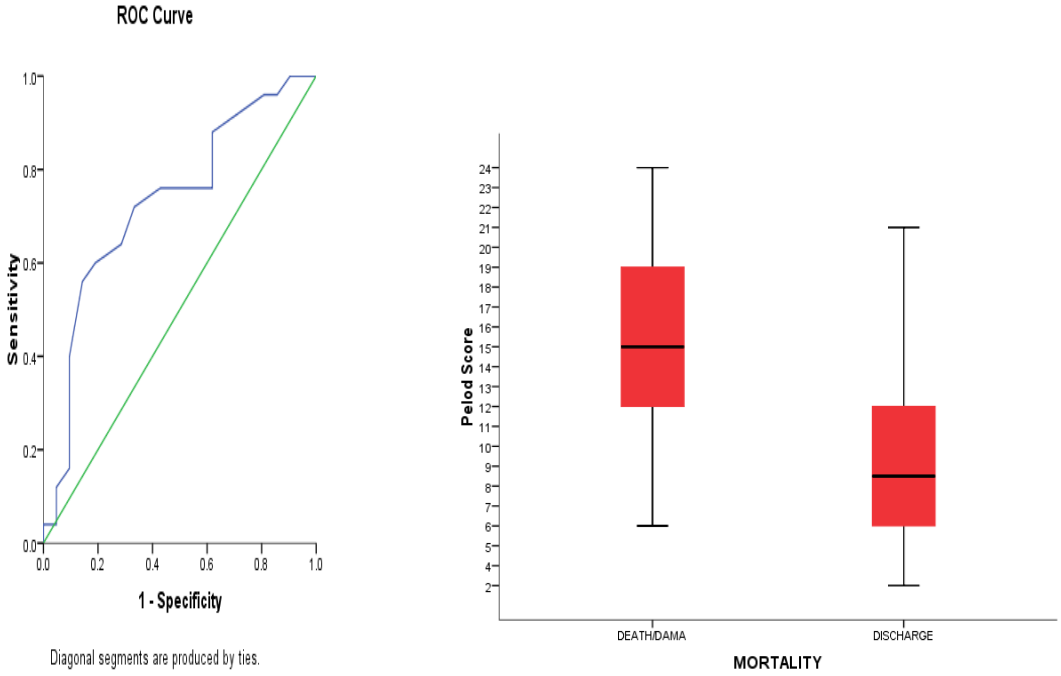


Figure 22.

PELOD proved to be a good score for assessing the risk for multi-organ dysfunction and predicting mortality.

AUC- 0.801, p value <0.001

The sensitivity was 30% and specificity was 69.6%.

PELOD Vs AKI:

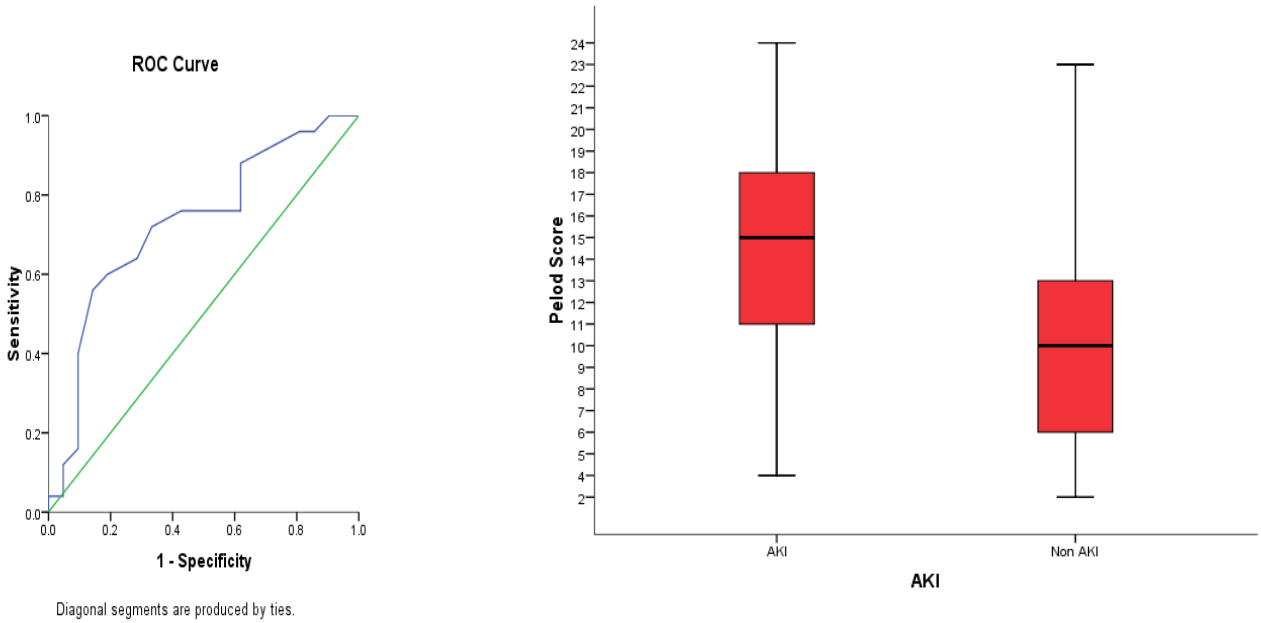


Figure 23.

PELOD was shown to be a useful score which could predict AKI.

(AUC-0.729, p value 0.008)

DISCUSSION:

Severe sepsis is one of the most common causes of admission to the Pediatric Intensive care unit. Multi-organ dysfunction is commonly seen in children with sepsis, acute kidney injury being the major complication amongst them. Early diagnosis of AKI may significantly improve the outcome and decrease mortality. Studies have reported that Sepsis-associated AKI contributes to a higher burden of mortality and morbidity in children with critical illness. There are several reports in literature of the risk factors of AKI and for early recognition of renal injury. There is an ongoing search for a good biomarker which can detect AKI early in the setting of Sepsis associated AKI and predict its outcome.

This study is a prospective observational study performed in the 11 bedded Pediatric Intensive Care unit of a tertiary hospital Christian Medical College Vellore from January to August 2017. The profile of children admitted with severe sepsis was studied. The standard definition laid by the International Consensus definition for Pediatric Sepsis was applied. All those children who fulfilled these criteria during the study period were recruited. The incidence, risk factors and outcome of acute kidney injury as defined by the AKIN criteria was studied and compared to the various diagnostic tools of acute kidney injury. The PELOD (pediatric logistic organ dysfunction) score was used to assess the severity of organ dysfunction (MODS) and

assess the risk of mortality in all patients. This score was done every day from the point of severe sepsis till the time of discharge or for the first 5 days whichever was earlier. All patients were managed as per the surviving sepsis guidelines. The end point of the study was when the patient was discharged/ died.

INCIDENCE OF SEVERE SEPSIS:

The number of admissions to the Pediatric Intensive Care Unit during the study period between January 2017 and August 2017 was 650. Of the total number of admissions, 49 (7.5%) had severe sepsis. Excluding 2 children who died within 12 hours of admission without any recorded urine output, we had 47 children who formed the study group. This group was statistically analysed.

The incidence of severe sepsis during this period was 7.5%. This was compared with other studies reported in literature. Rakesh Lodha et al in a study done in PICU in Delhi, observed that the incidence of severe sepsis and septic shock was relatively low in children admitted in the western pediatric intensive care units(2-4%), but the figures are much higher (40-67%) for Indian PICUs.

PROFILE OF CHILDREN WITH SEVERE SEPSIS:

The demographic profile of our patients with severe sepsis was studied. It was noted that 46.8% (22/47) were between 1-5 years of age, 40.4% (19/47) were above 5 years of age and 12.8% (6/47) were under 1 year of age. The mean age was 56.33 months (range 1-230 months). Male to female ratio was almost equal in our study 1:1(Table 1). In the

study by Kurade et al in a PICU in Maharashtra, over a period of 3 years, children aged 1 month to 18 years with septic shock were analysed. Of these, 56.3% (53/1035) had septic shock. The mean age was 3 years (range 1m-14 yrs). They reported majority of the children to be infants (25/43 (48.83%)). Children over 1 year constituted 18/43 (41.8%) of the remaining. The Male-female ratio in their study was also 1:1:1. While their study reported sepsis in predominantly infants, our study reported higher incidence in children between 1-5 years. The reason for this is not very clear but could be due to differences in the disease profile at different places and times of the year. While our study was limited to 7 months, Kurade et al studied Sepsis over a 3 year duration allowing for a more varied disease profile. In the previously published study by Agarwal et al on the clinical profile and outcome of acute renal failure in south Indian children from our centre in 2003, 44 children (22%) had proven sepsis and another 22% were suspected to have sepsis. Presentation with septic shock was noted in 45% of the patients.

Almost 2/3rd of the children 36 (76.6%) of the children were from Tamil Nadu, 6(12.8%) were from Andhra Pradesh and 5(10.6%) were from other states of India.

The association of nutritional status with the outcome of severe sepsis was also studied. We found that 24/47(51.1%) children had normal nutritional status. 21.1% (10/47) had moderate malnutrition as defined by WHO classification based on standard deviation scores and 27.6%(13/47) had severe malnutrition. Almost half of the patient population had malnutrition in our study (48.9%) 23/47. (Table 13).

Clinical presentation and symptoms with which the children were brought to hospital was looked at. Fever was the commonest symptom in our study noted in 76.6%(36/47) of children followed by altered sensorium in 44.7%(21/47), seizures 29.8%(14), bleeding manifestations 4.3% (2), decreased urine output 4.3% (2) and rash 2.1%(1) (Table 2 &Fig 2). Mean duration of symptoms was 5.5 days. A similar observation was reported by Kurade et al in his study where fever was the commonest presenting symptom in 27(62.79%) followed by altered mental status in 13(30.23%). Others included breathlessness in 23.25%, cough in 18.60%, vomiting and abdominal distension in 9.3% each. Mean duration of symptoms was 6.4 days in their study.

The various clinical signs at presentation in our study included tachycardia, tachypnea, hypotension, low GCS and temperature instability. Of these tachypnea and hypotension were the commonest sign which was seen in 72.3% (34/47) each. This was followed by low GCS 59.5% (28/47), hyper/hypothermia 51.1% (24/47) and tachycardia 44.6% (21/47).(Table 5 &Fig 5). Similarly in the Kurade et al study, hypotension was the commonest clinical finding reported in 81.39% (35/43), tachycardia and tachypnea in 74.41%(32/43) each and temperature instability in 62.79%(27/43), and respectively. The above mentioned presenting symptoms were statistically analysed age >1 year 41/47(OR:7.059;95% CI:0.755-65.983), fever present in 36/47(OR:4.190;95% CI:0.948-18.529), oliguria present in 2(OR:1.957;95%CI:1.470-2.604), seizures present in 14/47(OR:1.255;95% CI:0.356-4.422), altered sensorium in 21/47(OR:1.33;95% CI:0.419-4.239), bleeding manifestation present in 2/47(OR:0.875;95%CI:0.051-14.872).

(Table 15). However it was found that only oliguria (OR 1.957; 95% CI: 1.470-2.604), was found to be statistically significant in our study. (Table 15).

The various investigations at presentation were analysed. The commonest finding was of hypoalbuminemia in 55.3% (26/47) of the children. This was closely followed by anaemia in 31.9%(15/47),grossly deranged liver enzymes in 34%(16/47), thrombocytopenia in 29.7%(14/47) and coagulopathy (PT>22secs, APTT> 57 secs) in 17%(8/47). Leucopenia was present in 10.6% (5/47) and elevated total bilirubin (>4mg/dl) levels was present in 6.3%(3/47), Mean leucocyte count was 12,149(5900-18,082)/ mm^3(Table 6). Deranged renal function tests was present in as many as 15/47(31.9%). In the Kurade et al study deranged liver enzymes was present in 86.04%, coagulopathy was seen in 60.41%, thrombocytopenia in 55.81%, anaemia in 27(62.7%), leucopenia in 13.95% and the least common was deranged renal function tests present in 6(13.95%). These results are quite in contrast to what we found in our study.

In our study, the following parameters were studied and were statistically analysed to look for significance, tachycardia present in 36/47(OR:4.19;95% CI: 0.948-18.529), tachypnea present in 21/47(OR:2.727;95% CI:0.825-9.011), hypotension present in 24/47(OR:1.816;95% CI:0.274-12.014), temperature instability present in 36/47(OR:4.190;95% CI:0.948-18.529), GCS<15 present in 25/47(OR:1.33; 95% CI:0.419-4.239), anaemia present in 15/47(OR:0.456 ; 95% CI:0.131-1.594), thrombocytopenia was present in 14/47(OR:1.255; 95% CI:0.356-4.422), elevated liver

enzymes present in 38/47(0.648; 95% CI:0.150-2.794). (Table 15). None of the above parameters were found to be statistically significant in our study.

In the study done by H.I. Rady et al in PICU in Mounira Pediatric hospital, Cairo, it was found that the mortality was increased in patients with fever and hypothermia (OR-5.9; specificity 99.4). Mortality was high with deranged liver enzymes >250IU/L (OR-3.6; ALT 95% CI: 47.86-155) and was double in patients with PT>22 secs or PTT > 57secs and was 100% in patients who needed anti-coagulation(post-cannulation thrombosis). However of these, none of the lab parameters were found to be statistically significant in our study. Bailey et al has shown that coagulopathy was a risk factor for acute Kidney injury and not as a predictor of outcome in children with shock. In our study 3 children required anti-coagulation due to post-cannulation thrombosis and mortality was 100% in them.

All 47 children required inotropic support to maintain a normal blood pressure in our study. Of these, 63.8% (30/47) children required inotropic support for < 72hrs and 36.1% (17/47) required for > 72 hours. Of the 47 children, almost half 46.9% (22/47) required ventilation for <72 hours, one third 34% (16/47) required ventilation for >72 hours. Prolonged need for inotropic support (OR:2.4;95%CI:0.202-28.451) and invasive ventilator support (OR:0.508;95% CI:0.122-2.107) were management strategies associated with poor outcome. However in our study they were not statistically significant.(Table 15).

The mortality of severe sepsis in our study group was 51.1% (24/47) (comprising of children who died and were discharged against medical advice). In the Kurade et al study the mortality rate was higher at 60.46%. The literature reports high mortality rate of over 50% in most pediatric patients with septic shock. An Indian study from PGI, Chandigarh also reported high (65.8%) mortality rate in fluid refractory septic shock.

In another study done by Gurpreet et al in a PICU in Haryana noted a mortality rate of 45%, in our study the mortality rate was 51.1%. The higher mortality rate was probably due to the fact that our centre being the prime referral centre for sick patients from surrounding districts, the patient population caters to all strata of socioeconomic status of both rural and urban districts of Tamil Nadu. Other Indian studies have reported mortality rates of 47% from Punjab, 50% from AIIMS, Delhi, 58% from Rohtak, Haryana. Our findings are similar to other Indian studies suggesting a severe adverse outcome irrespective of the underlying predisposing factors and quality of critical care available. Rica et al in his study on the epidemiologic trends of severe sepsis in western countries observed a mortality rate ranging between 20-50%, In the US, mortality due to severe sepsis had a relative reduction from 51% to 24%. French ICUs report a mortality rate ranging from 35% to 56%. Recent retrospective studies from Australia and New Zealand reported a mortality rate between 18.4 % -35%.

INCIDENCE OF ACUTE KIDNEY INJURY:

The incidence of Acute Kidney injury in children with severe sepsis in our study was 53.1% (25/47). Of the 25 with acute kidney injury classified as per the AKIN criteria , 31.9%(15/47) were in Stage 1, 8.5%(4/47) were in Stage 2 and 12.8%(6/47) were in Stage 3(Figure 12). Overall risk of acute kidney injury in our Pediatric Intensive care unit during the eight month period was about 3.8%(25/650). The mortality rate in children with sepsis associated AKI (SA-AKI) in our study was 16/24 (66.7%).

Prowle et al reported that sepsis associated acute kidney injury accounted for 50% of all cases of AKI in ICU. He stated that 50% of patients with sepsis associated AKI survive to hospital discharge and among those who survive approximately 85-90% recover to dialysis independence. In our study similar trend was observed, 50% of them with SA-AKI survived and mortality was 50%.

Devarajan et al did a retrospective study in Cincinnati Children's Hospital for Acute Care Nephrology on 77 children with sepsis associated AKI. They noted that the incidence of severe AKI was 75% considering all stages taken together. The overall mortality rate was 33.7%. In this study AKI was defined based on pRIFLE criteria.

Fitzgerald et al did a prospective cross-sectional point prevalence study done in 128 PICUs in 26 countries, on children with severe sepsis as part of the Sepsis Prevalence Outcomes and Therapies study. They noted that 493 children had severe sepsis out of 6925 (7.12%) screened over a period of 5 days. Out of these 493 children 102(21%) had

AKI, amongst which 79 %(391/493) had stage 1 AKI and 20.6% (102/493) had stage 2-3, based on KDIGO criteria. The mortality rate in this study was 64%. The authors concluded that children with sepsis-associated severe AKI had more than double the odds of death or new moderate disability at hospital discharge than children with severe sepsis with no/mild AKI. Severe AKI was proven to be an independent risk factor for death/moderate disability (adjusted odds ratio, 2.5; 95% CI: 1.5-4.2; p=0.001).

The varied incidence of AKI in different studies and mortality rate of AKI could be due to the different definitions used for the diagnosis of AKI. Our study defined AKI as per the AKIN criteria whereas several of the above mentioned studies defined AKI based on calculated GFR and baseline creatinine. However, on several occasions, baseline creatinine is unknown in clinical practice.

OUTCOME OF ACUTE KIDNEY INJURY:

The outcome of acute Kidney injury in our study group was evaluated. Children who died and those who were discharged against medical advice were considered together as poor outcome and compared against the children who improved and were discharged. Mortality among children with Acute Kidney was 64% (16/25). (Table &Fig 17). The overall mortality was 51.1% (24/47) amongst children with severe sepsis in our Pediatric Intensive Care unit. In our study the mortality rate was double (2.02) in children with acute kidney as compared to those without acute kidney injury.(66.7% vs 33%).

A retrospective analysis by Plotz et al in children admitted with severe septic shock from 1998 to 2004 in Netherlands showed that mortality rates were significantly higher in the acute renal failure group as compared to the non acute renal failure group (57.1% vs. 6.7%). Our study also reported a very high mortality rate as in the above study. The study design was also similar with inclusion criteria of children with fluid and dopamine resistant shock and definition of acute renal failure as deterioration of renal function including the need for renal replacement therapy. This may be explained by the fact that mortality rate of severe sepsis as such, with or without acute kidney injury in Indian population is very high (almost 50%-60%) as compared to the western population(18.5-34%).

Plotz B et al in his retrospective descriptive cohort study to evaluate the practicability of pRIFLE criteria in diagnosing AKI and analysis of factors associated with poor outcome found a five times higher mortality in children with acute kidney injury as compared to those without acute kidney injury(25% vs 5%). His study was only on children with respiratory failure requiring mechanical ventilation for >4 days. As our study dealt with Sepsis with or without acute kidney injury, mortality is very high compared to theirs.

Bailey et al did a one year prospective study on all Canadian children admitted into the Pediatric intensive care unit found a 11 fold increase in mortality in the AKI group as compared to the non AKI group (27.3% vs 2.5%). He reported that the presence of Multi-organ dysfunction and high PRISM scores in the Acute renal failure group could have contributed to the higher mortality in the AKI group. Our study showed only a **2**

times increase in mortality in the acute kidney injury group**.** The reason for this difference could be that our study group included only children with fluid resistant shock.

In the SPROUT study Fitzgerald et al studied children with severe sepsis and found that severe AKI was present in approximately 20% pediatric patients with severe sepsis. The study showed that mortality rate in children with severe AKI was more than twice as high as those with no/mild AKI (64% vs 30%; $p<0.001$). Severe AKI was shown to be independently associated with death or new moderate disability (adjusted OR, 2.5; 95% CI, 1.5-4.2, $p=0.001$). Our study reported twice the increased risk of mortality in sepsis associated AKI (66.7% Vs 33.3%).

Alobaidi et al also studied in children with sepsis associated AKI and reported a higher incidence in critically ill children. Another large study done in 57 adult ICUs in Australia and New Zealand SA-AKI identified AKI in 11.7%.

The Beginning Ending Supportive Therapy for the Kidney, a large prospective observational study of more than 29,000 patients, reported an AKI incidence of 5.7% with SA-AKI being the most common etiology (47.5%). Analysis of 276,731 admissions to 170 adult critical care units of the UK Intensive Care National Audit and Research Centre identified con-current sepsis and AKI in 8246 ICU admissions in the first 24 hours.

Retrospective studies in primarily sepsis cohorts also have reported a high concurrence of SA-AKI. More than 60% of 4532 patients with septic shock from 1989 to 2005 suffered

AKI. In another cohort, AKI was present in 17.7% of 722 patients admitted to an ICU specifically for infectious disease.

RISK FACTORS FOR AKI:

The various demographic characters were analyzed to look for significant risk factors for Acute kidney injury. The mean age of the study group was 52.35months with a range of 5 months to 18 years in our study (Table 12). Age group between 1-5 years (n=14),56%(14/25), was observed as a risk factor for AKI in our study. Fever was a common presentation amongst the children with AKI (22/36, 61%), followed by altered sensorium 12/21(57%), seizures 8/14(57%), oliguria 2/2(100%) and bleeding manifestation 1/2(50%). Amongst the clinical signs tachypnea was very common in the AKI group 14/21(66.7%), followed by tachycardia 22/36(61%), hypotension 19/34(55%). Amongst the various lab parameters coagulopathy was commonly present in the AKI group 5/8(62%). In the AKI group 10/17(62%) required prolonged invasive ventilator support and 12/17(70%) required prolonged duration of inotropic support as compared to the non-AKI group (Table 13).

Amongst the presenting symptoms oliguria (2/47, 4.3%) was considered a statistically significant risk factor for AKI (OR: 1.957;95% CI:1.470-2.604). (Table 15). The other lab parameters which was statistically analysed were not found to be significant.

Simon et al did a study on the incidence, risk factors and outcomes of acute kidney injury in critically ill children and observed that AKI occurred in 42% (130 patients) . Of these,

55% of the children <2 years had AKI as observed in his study as compared to < 13 years (27%) and >13 years(37%). Bailey et al reported age > 12 years in acute renal failure in critically ill children to be a significant predictor of renal failure. In our study, age group between 1-5 years (n=14), 56% was considered risk factor for AKI. (Table 13).

Among the symptoms at presentation, only oliguria (OR: 1.957; 95% CI: 1.470-2.604) was found to be a significant risk factor for acute kidney injury.(Table 15). Hypotension, tachycardia, tachypnea and temperature instability were analysed and were not found to have a significant correlation (Table 15). Thrombocytopenia, abnormal counts, coagulopathy and elevated liver enzymes also did not reach statistical significance (Table15). Prolonged need for inotropic support>72hrs and invasive ventilator support >72hrs also did not show a significant correlation.

Bailey et al in his study found hypoxemia, hypotension, thrombocytopenia age > 12 years and coagulopathy to be significant risk factors for acute renal failure in critically ill children.

Riyuzo et al studied the predictive factors of mortality in pediatric patients with acute renal injury associated with sepsis and identified the risk factors of mortality as PICU length of stay (OR=0.615, SE=0.1377, 95% CI=0.469-0.805, p=0.0004); invasive mechanical ventilation (OR=14.599, SE= 1.1178, 95% CI= 1.673-133.7564, p=0.0155); need for dialysis(OR =9.714, SE= 0.8088, 95% CI=1.990-47.410, p=0.0049) and hypoalbuminemia (OR= 10.484, SE= 1.1147, 95% CI= 1.179-93.200, p=0.035).

Medina et al in the Spanish prospective study to analyze the characteristics of acute renal failure in critically ill children found hypovolemia (50%) and hypotension (37%) as significant risk factors.

DIAGNOSIS OF AKI

There were 25 patients who fulfilled the diagnostic criteria for AKI. They were eligible for testing the various tools for detection of AKI. The mean age group was 52.35 months with a range of 5 months-18 years. There were 12 males (50%) and 13 females (56.5%). Male to female ratio was 1:1.1. Mean weight was 18.906 kg with a range of 2.9-51.0 kg. Mean height was 103.13cm with a range of 47cm to 155cm.

The creatinine in the group ranged from 0.7mg/dl to 3.68 mg/dl with a mean of 0.6679mg/dl. Creatinine clearance by Modified Schwartz formula ranged from 22 to 345 ml/min/1.73 m^2 with a mean of 120.055. Of the 47 children analysed 22(46.8%) had normal renal functions and 25(53.1%) had acute Kidney injury. 15(31.9%) were in stage1, 4 (8.5%) in stage2, 6(12.8%) were in stage 3. The mortality in the AKI group was 68% (17/25) while the rest 32% (8/25) were discharged with normal renal functions and with no residual kidney disease.

BIOMARKERS FOR SEPSIS ASSOCIATED AKI:

L-FABP values ranged from 0.7 to 487 ng/dl with a mean of 85ng/dl. Median L-FABP level at baseline was 1.3 times more in the AKI group than in Non-AKI group.

However L-FABP levels at baseline and at 48hrs was not a significant predictor of AKI (p value 0.778 and 0.946). It had a 26.1% sensitivity and 71.4% specificity in predicting AKI.

At admission, L-FABP level was able to differentiate survivors and non-survivors with a p value of 0.048**.** The L-FABP levels were repeated at 48 hours and was compared amongst the survivors and non-survivors. However at 48 hours, when compared between the survivors and non survivors, it could not predict mortality (p=0.667).

L-FABP was also compared with PELOD score for assessing multi-organ dysfunction and mortality. Mean L-FABP levels were compared against PELOD score of >10 – though it had a fairly good predictability for multi-organ dysfunction (MODS) and mortality; it did not reach statistical significancet (p = 0.07).

An ROC was drawn out and it was demonstared that L-FABP at admission (baseline) was found to be a good predictor of mortality with a sensitivity of 40% and specificity of 88.2% AUC- 0.6910, p value 0.048.

Similarly, PELOD score showed a significant ability to predict multi-organ dysfunction and mortality.**AUC- 0.801, p value <0.001.** The sensitivity was 30% and specificity was 69.6%. PELOD score was able to significantly predicting AKI. (AUC-0.729, p value 0.008).

In a cross-sectional study Ferguson et al studied the comparative values of multiple biomarkers used in the diagnosis of AKI. In a total of 92 patients with established AKI, they showed that the diagnostic ability of L-FABP in diagnosing AKI in hospitalized patients was very good (ROC-AUC 0.93), as compared to other well-described biomarkers of AKI including NGAL (0.92), KIM-1(0.89), NAG(0.89) and IL-18(0.83). In this study L-FABP emerged as a significant predictor of RRT (p=0.02) and the composite end point of death/RRT (p=0.03).

However in our study L-FABP failed to prove its ability in predicting AKI (p=0.778). (Table 22). AUC-ROC curve for L-FABP done at baseline was (0.472) and AUC-ROC curve for L-FABP at 48 hr was (0.507). (Figure 20).

In the Ferrguson et al study, Urine L-FABP ≥ 370ng/ml (RR 2.76 ;95% CI:1.22-6.25), was identified as a significant risk factor of mortality in children with sepsis. Diagnostic performance of first urine L-FABP was analysed using ROC-AUC and was found to be 0.647(95% CI: 0.500-0.795), which showed that urinary L-FABP may be a useful predictor of mortality in septic children. These results obtained were similar to our study.

From our study, we can infer that L-FABP could be a useful biomarker to predict mortality and multi-organ dysfunction in children admitted with sepsis. However it was not useful in predicting AKI. PELOD was confirmed to be a good score to assess multi-organ dysfunction and AKI.

SUMMARY:

1. There were 650 admissions to the PICU during the study period January 2017 to August 2017. Following the inclusion criteria, 47 children were studied further.
2. The incidence of severe sepsis during the study period was 47/650 (7.5%).
3. The mean age of children in our study was 56.33 months with a range of 1 to 230 months. Severe sepsis was more common between the age group of 1-5 years which constituted 41.8% of the study population.
4. Male: Female ratio was 1:1.1.
5. 51% had normal nutritional status. Of the remaining 49%, 21.3% had moderate malnutrition and 27.7% had severe malnutrition.
6. Fever was the commonest symptom in 76.6% followed by altered sensorium (44.7%), seizures (29.8%), decreased urine output (4.3%), bleeding manifestation (4.3%) and rash (2.1%). 29.7% were hospitalized elsewhere prior to admission.
7. Amongst the clinical signs tachypnea and hypotension were present in 72.3% each followed by low GCS (59.5%), temperature stability (51.1%) and tachycardia (44.6%).
8. Hypoalbuminemia (55.3%) was the commonest lab parameter, followed by elevated liver enzymes (34%), anaemia (31.95), thrombocytopenia (29.7%), coagulopathy (17%) and hyperbilirubinemia (8.5%).
9. Oliguria (odds ratio 1.957, 95%CI: 1.470-2.604, p= 0.043) was a significant risk factor for AKI and poor outcome among children with severe sepsis.

10. Of the total, 62% of the children with severe sepsis required invasive ventilation for >72 hours and 70% of them required inotropic support for > 72 hours.

11. The mortality of severe sepsis in our study group was 51.1% (25/47).

12. The incidence of Acute Kidney Injury in children with severe sepsis was 53.1% (25/47).

13. Of the 25 with acute kidney injury classified as per the AKIN criteria , 31.9%(15/47) were in Stage 1, 8.5%(4/47) were in Stage 2 and 12.8%(6/47) were in Stage 3.

14. Mortality in children with Acute Kidney Injury was 66.6% (16/24). The overall mortality due to SA-AKI was 51% (24 / 47)

15. Hypotension (p value 0.536), tachycardia (p value 0.05), lab parameters like anaemia (p value 0.219), thrombocytopenia (p value 0.724), coagulopathy (p value 0.651), elevated liver enzymes (p value 0.662) were not found to be statistically significant.

16. L-FABP at admission (baseline) was 1.3 times more in the AKI group than in Non-AKI group

17. Liver type Fatty Acid Binding Protein (L-FABP) had a sensitivity of 26.1% and specificity of 71.4% in diagnosing AKI our study.

18. At admission, L-FABP level was able to differentiate survivors and non-survivors with a p value of 0.048. (p=0.667). It was a good predictor of mortality with a sensitivity of 40% and specificity of 88.2% AUC- 0.6910, p value 0.048.

19. Repeat L FAB levels between survivors and non survivors at 48 hours, L-FABP repeat L-FAB levelscould not predict mortality. (p=>0.05)
20. PELOD score had a significant correlation with the risk for multi-organ dysfunction and could predict mortality (AUC- 0.801, p value <0.001). The sensitivity was 30% and specificity was 69.6%.
21. PELOD score was significant in predicting AKI (AUC-0.729, p value 0.008).

CONCLUSION:

1. Incidence of severe sepsis was 7.5%
2. The incidence of Sepsis-Associated Acute Kidney Injury was 53.1%.
3. Mortality of severe sepsis was 51.1%. It remains high inspite of improvement in treatment strategies and critical care facilities.

   Mortality in AKI was 2 times more in children with AKI vs non AKI (66.7% Vs 33%).
4. L-FABP was not a good biomarker tool to predict AKI.
5. Baseline L-FABP level (at admission) was able to differentiate survivors and non-survivors with a p value of 0.048, sensitivity of 40% and specificity of 88.2%. However repeat L –FAB samples at 48 hours could not add benefit as it could not predict non survival.
6. PELOD was confirmed to be a good score to assess mortality(p value <0.001) and AKI (<0.008).

LIMITATION:

1. Small sample size in studying the utility of L-FABP – a larger study may have provoded more accurate results.
2. Doing L- FABP levels on controls would have added more validity to the study.

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ANNEXURES:

Patient Information Sheet – Urinary FABP in severe sepsis

Dear Parents ,

I am Dr. Merlyn, and I am doing my post- graduation in Pediatrics in Christian Medical College, Vellore. I am doing a research through which we aim to determine the complications associated with severe sepsis(Infection). Also the cause of death in sepsis, and the role of a urine test L-FABP(Fatty acid binding protein) in detecting the risk of death earlier.

Myself and my research team would like to invite you to take part in this study. Once you give your consent you will be included in the study . I would like to ask a few questions pertaining to my questionnaire which would contain general information about your child and also questions regarding cause of severe infection and complications. I would collect a urine sample(after admission at 0 hour, then at 24 hours and after 48 hours) of your child at admission that would help us with our study. The sample collected will be processed later which will help in future reference and study.

What is the purpose of the study?

Severe infection is very common in children and associated with many complications and can even lead to death. Hence it is necessary to detect the severity earlier so that we can act earlier. This study will help in determining the complications and probability of mortality earlier by doing a simple urine test at the time of admission itself, to see it the levels correlate with the severity of the infection.

Why are you invited?

We would like to know the complications associated with severe infection and the reason for such severity only in certain children. By doing the special urine test earlier during the disease course, and based on the levels we obtain, we might come to know the severity of the disease condition quite earlier and act earlier. Since your child is suspected to have a severe infection we would like your child to participate in the study.

Do I have to take part?

No. You don't. You may choose not to have your child participate in this study.Choosing to participate or not will not affect either your own or your child's future treatment at the Centre here in any way. You and your child will still have all the benefits that would otherwise be available at this Centre.

What will happen to me if I take part?

I would like to ask a few questions pertaining to my proforma which would contain general information about your child and also questions regarding your child's severe infection and the associated complications. I would also be looking at your child's blood tests and urine test

reports during admission to determine the status of severity of the infection. Along with the routine urine tests I would like to collect an extra urine sample for the sepical test that I would like to perform pertaining to my study. The knowledge gained through this study will help in future as a reference for early intervention and treatment in children with severe infection.

What are the possible benefits of the study?

The knowledge obtained from the study will help in future for predicting the severity of the infection and complications and the chance of mortality so that we can intervene earlier.

Reimbursements

Your daughter/son will not be provided with any payment to take part in the research.

Will my taking part in the study be confidential?

Your individual answers will not be shared with others. The information that we collect from this research project will be kept confidential. Information about your child that will be collected for the research prupose will be put away and no-one but the researchers will be able to see it. It will not be shared with or given to anyone except the research team.

What will happen to the results of the research study?

At the end of the study, we will be sharing what we have learnt with the community. The information that you share about your child will not be revealed outside the research team, and nothing will be attributed to him/her by name. We will also publish the results in order that the results gained from this study will benefit the others.

Who to Contact?

If you wish to ask questions later, you may contact:
Dr. Merlyn Nisha. J
Department of Pediatrics
Christian Medical college,
Vellore.
0416-2283348/984358731
Merlynnisha45@gmail.com

Informed Consent form to participate in a research study

Study Title:
Urinary FABP as a mortality predictor in children with severe sepsis

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study.

(ii) I understand that by answering the questions put forward by the doctor, I am giving my consent as a participant volunteer in this study and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand the basic nature of the study and agree that any potential risks are exceedingly small. I also understand the potential benefits that might be realized from the successful completion of this study.

(iv) I am aware that the information is being sought in a specific manner so that no identifiers are needed and that confidentiality is guaranteed.

(v) I understand that researcher, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(vi) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(vii) I agree to take part in the above study. [ ]

I am aware that certain blood and urine tests will be done at admission the results of which will be analysed. I am also aware that blood and urine samples will be stored for future study and reference.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: ___ Signature

Informed Assent Form for Children who are invited to take part in the study(> 8 years)

Name of Principle Investigator: Dr.Merlyn Nisha. J

Name of Organization: Christian Medical College,Vellore

Name of the research: urinary FABP as a predictor of mortality in children with severe sepsis

I have read the information sheet . I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research.

Print name of child _____

Signature of child: _____

Date:_____

day/month/year

In case of any query kindly contact

Dr.Merlyn Nisha

Department of Paediatrics

Christian Medical college

Vellore

0416-2283348/9843587231

ஆய்வுதலைப்பு: urinary FABP as a predictor of mortality in children with severe sepsis

ஆராய்ச்சிஎண்: _____

பொருளின்தலைப்பெழுத்துக்கள்:, _____

பொருளின்பெயர்: _____

(தலைப்பு)

நான்இந்ததகவலைவாசிதுக்கொண்டேன்.(எனக்குஇந்ததகவல்வாசிக்கப்பட்டது).என்கேள்விகளுக்குபதில்பெற்றுக்கொண்டேன். இன்னும் இருந்தால் நான் பின்னர் கேள்விகளை கேட்க முடியும் என்று எனக்கு தெரியும்.

நான் ஆராய்ச்சியில் பங்கேற்க ஒப்புக்கொள்கிறேன் .

குழந்தை அச்சிட பெயர் _____

குழந்தை கையொப்பம்: _____

நாள்: _____ நாள் / மாதம் / ஆண்டு

PROFORMA:

L-FABP AS A MORTALITY PREDICTOR IN SEVERE SEPSIS

Name- Hospital number - Date-

Sex- Boy / Girl Date of birth - Age in years -

Address-

Weight - kg Height- cm

MUAC :

Prior hospitalization – Yes / No- if Yes - days

HISTORY:

1.FEVER - ☐ YES ☐ NO

2. DURATION ☐ DAYS

3.RASH ☐ YES ☐ NO

5.BLEEDING MANIFESTATION ☐ YES ☐ NO

6. DECREASED URINE OUTPUT YES ☐ NO ☐

7.BREATHLESSNESS ☐ YES ☐ NO

8.IMPAIRMENT IN SENSORIUM ☐ YES ☐ NO

9. SEIZURES YES ☐ NO ☐

DAILY MONITORING SHEET:

	AT ADMISSION(WARD)	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5					
TEMPERATURE											
HEMOGLOBIN/PCV											
PLATELETS											
PT											
APTT											
TOTAL/DB BILIRUBIN											
ALBUMIN											
OT/PT											
CRP											
SODIUM											
POTASSIUM											
CREATININE											
UREA											
INOTROPES											
BLOOD TRANSFUSION											
URINE OUTPUT											
CREAT. CLEARANCE(SWARTZ)											

14 . SHIFTED TO PICU/HDU ☐ YES ☐ NO

15. ON DAY ---------- OF ADMISSION

16. PELOD SCORE

ORGAN DYSFUNCTION AND VARIABLE	SCORE DAY 1	SCORE DAY 2	SCORE DAY 3	SCORE DAY 4	SCORE DAY 5
NEUROLOGIC:					
1. GCS					
2.PUPILLARY REACTION					
CARDIOVASCULAR					
1. LACTATEMIA (mmol/L)					
2. MAP mmhg					
RENAL					
1. CREATININE					
RESPIRATORY					
1. PaO2					
2.PaCo2					
3. INVASIVE VENTILATION					
BLOOD					
1. TOTAL COUNTS					
2.PLATELETS					

17.Urinary FABP at admission- ng/dl

18. CORRELATION OF URINARY FABP AND PELOD SCORE:

PELOD SCORE	
URINARY FABP(0 HOUR SAMPLE)	

19. OUTCOME -Death/discharged

slno	Specimen ID	Time	name	hospno	date	bleeding	urine	Remark
19	P39-MN-01	First sample	nithrathan	528634g	1/9/2017	2	2	
	P39-MN-02	Second sample	nithrathan	528634g	1/9/2017			
21	P39-MN-03	First sample	karthikeyan	541480g	1/11/2017	2	2	
	P39-MN-04	Second sample	karthikeyan	541480g	1/11/2017			
15	P39-MN-05	First sample	dhiya	542260g	1/21/2017	2	2	
	P39-MN-06	Second sample	dhiya	542260g	1/21/2017			
22	P39-MN-07	First sample	jabastin	690302g	1/22/2017	2	2	
	P39-MN-08	Second sample	jabastin	690302g	1/22/2017			
27	P39-MN-09	First sample	gowtheeswaran	083010f	1/23/2017	2	2	
	P39-MN-10	Second sample	gowtheeswaran	083010f	1/23/2017			
11	P39-MN-11	First sample	jeevaraj	528711g	1/24/2017	2	2	
	P39-MN-12	Second sample	jeevaraj	528711g	1/24/2017			
12	P39-MN-13	First sample	srinithi	543017g	1/27/2017	2	2	
	P39-MN-14	Second sample	srinithi	543017g	1/27/2017			
14	P39-MN-15	First sample	hari priya	551070g	1/28/2017	2	2	
	P39-MN-16	Second sample	hari priya	551070g	1/28/2017			
40	P39-MN-17	First sample	shreven durga	696656f	1/29/2017	2	2	
	P39-MN-18	Second sample	shreven durga	696656f	1/29/2017			
46	P39-MN-19	First sample	baby of gayathri	515841g	2/10/2017	2	2	
	P39-MN-20	Second sample	baby of gayathri	515841g	2/10/2017			
5	P39-MN-21	First sample	deepika	365173d	2/16/2017	2	2	
	P39-MN-22	Second sample	deepika	365173d	2/16/2017			
45	P39-MN-23	First sample	sakthivel	192055d	2/17/2017	2	1	
	P39-MN-24	Second sample	sakthivel	192055d	2/17/2017			
28	P39-MN-25	First sample	balaji	551876g	2/18/2017	2	2	
	P39-MN-26	Second sample	balaji	551876g	2/18/2017			
38	P39-MN-27	First sample	tharuniya	551837g	2/20/2017	2	2	
	P39-MN-28	Second	tharuniya	551837g	2/20/2017			

		sample						
7	P39-MN-29	First sample	mohammed hayath	551902g	2/20/2017	2	2	
	P39-MN-30	Second sample	mohammed hayath	551902g	2/20/2017			
16	P39-MN-31	First sample	dharani	551547g	3/4/2017	2	2	
	P39-MN-32	Second sample	dharani	551547g	3/4/2017			
13	P39-MN-33	First sample	varshini	551574g	3/5/2017	2	2	
	P39-MN-34	Second sample	varshini	551574g	3/5/2017			
30	P39-MN-35	First sample	krithik roshan	253056g	3/6/2017	2	2	
	P39-MN-36	Second sample	krithik roshan	253056g	3/6/2017			
6	P39-MN-37	First sample	haniya	547166g	3/13/2017	2	2	
	P39-MN-38	Second sample	haniya	547166g	3/13/2017			
26	P39-MN-39	First sample	priyadarshini	551316g	3/15/2017	2	2	
	P39-MN-40	Second sample	priyadarshini	551316g	3/15/2017			
9	P39-MN-41	First sample	yamgo gamlin	835107g	3/30/2017	2	2	
	P39-MN-42	Second sample	yamgo gamlin	835107g	3/30/2017			
39	P39-MN-43	First sample	atiya	528828g	4/1/2017	2	2	
	P39-MN-44	Second sample	atiya	528828g	4/1/2017			
17	P39-MN-45	First sample	wasim	528908g	4/4/2017	2	2	
	P39-MN-46	Second sample	wasim	528908g	4/4/2017			
43	P39-MN-47	First sample	lithiya sri	567596g	4/10/2017	2	2	
	P39-MN-48	Second sample	lithiya sri	567596g	4/10/2017			
18	P39-MN-49	First sample	sumily dey	813438g	4/25/2017	2	2	
	P39-MN-50	Second sample	sumily dey	813438g	4/25/2017			
20	P39-MN-51	First sample	ridha taslen	957581f	5/18/2017	2	2	
	P39-MN-52	Second sample	ridha taslen	957581f	5/18/2017			
47	P39-MN-53	First sample	lokeshwaran	556374g	5/24/2017	2	2	
	P39-MN-54	Second sample	lokeshwaran	556374g	5/24/2017			
25	P39-MN-55	First sample	kavin	528035g	5/30/2017	2	2	
	P39-MN-56	Second sample	kavin	528035g	5/30/2017			

1	P39-MN-57	First sample	baby of vijayalakshmi	700215g	6/1/2017	2	2	
	P39-MN-58	Second sample	baby of vijayalakshmi	700215g	6/1/2017			
24	P39-MN-59	First sample	muzahidul	556361g	6/3/2017	2	2	
	P39-MN-60	Second sample	muzahidul	556361g	6/3/2017			
35	P39-MN-61	First sample	lesha	556578g	6/4/2017	2	2	
	P39-MN-62	Second sample	lesha	556578g	6/4/2017			
34	P39-MN-63	First sample	lakshitha	556590g	6/5/2017	1	2	
	P39-MN-64	Second sample	lakshitha	556590g	6/5/2017			
3	P39-MN-65	First sample	narasimah	556611g	6/6/2017	2	2	
	P39-MN-66	Second sample	narasimah	556611g	6/6/2017			
33	P39-MN-67	First sample	akash	638104c	6/6/2017	2	2	
	P39-MN-68	Second sample	akash	638104c	6/6/2017			
32	P39-MN-69	First sample	tharunika	999056f	6/10/2017	2	2	
	P39-MN-70	Second sample	tharunika	999056f	6/10/2017			
8	P39-MN-71	First sample	rithika	556570g	6/12/2017	2	2	
	P39-MN-72	Second sample	rithika	556570g	6/12/2017			
2	P39-MN-73	First sample	sai kiruthik	557806g	6/13/2017	2	2	
	P39-MN-74	Second sample	sai kiruthik	557806g	6/13/2017			
41	P39-MN-75	First sample	bismina	744822g	6/21/2017	2	2	
	P39-MN-76	Second sample	bismina	744822g	6/21/2017			
4	P39-MN-77	First sample	issa marya	321702g	6/24/2017	2	2	
	P39-MN-78	Second sample	issa marya	321702g	6/24/2017			
10	P39-MN-79	First sample	jeyan	556809g	6/24/2017	2	2	
	P39-MN-80	Second sample	jeyan	556809g	6/24/2017			
23	P39-MN-81	First sample	hemsai	577218d	6/26/2017	2	2	
	P39-MN-82	Second sample	hemsai	577218d	6/26/2017			
29	P39-MN-83	First sample	pirunishka	906177f	6/28/2017	1	1	
	P39-MN-84	Second sample	pirunishka	906177f	6/28/2017			
42	P39-MN-85	First sample	brindha	556926g	7/4/2017	2	2	

	P39-MN-86	Second sample	brindha	556926g	7/4/2017			
36	**P39-MN-87**	First sample	srija	556961g	7/6/2017	2	2	
	P39-MN-88	Second sample	srija	556961g	7/6/2017			
44	**P39-MN-89**	First sample	kauveri	556198g	7/10/2017	2	2	
	P39-MN-90	Second sample	kauveri	556198g	7/10/2017			
37	**P39-MN-91**	First sample	hemamalini	941946d	7/16/2017	2	2	
	P39-MN-92	Second sample	hemamalini	941946d	7/16/2017			
31	**P39-MN-93**	First sample	puvidharan	898987f	7/18/2017	2	2	
	P39-MN-94	Second sample	puvidharan	898987f	7/18/2017			

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CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Ref: IRB – A1 - 01.06.2017

July 19, 2017

Dr. Merlyn Nisha,
PG Registrar,
Department of Child Health - 2,
Christian Medical College,
Vellore 632 002

Ref: 1. IRB: 10471 dated: 05.01.2017

Dear Dr. Merlyn Nisha,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following amendment for the study titled "A study of the clinical profile of Severe Sepsis in children and the association, if any, of Urinary Liver-type Fatty Acid Binding Protein (L-FABP) with mortality, morbidity and diagnosis of acute kidney injury" on June 01st 2017.

1. Three co-investigators are added Dr. Ebor Jacob, Professor, Paediatric Intensive Care Unit 2. Dr.Pragatheesh, Paediatric Intensive Care Unit 3. Dr. Vinoi, Nephrology.

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on June 01st 2017 at 12.45 Pm in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. RatnaPrabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology,CMC, Vellore	Internal, Pharmacologist

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. RekhaPai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. SowmyaSathyendra	MBBS, MD (Gen. Medicine)	Professor, Medicine III, CMC, Vellore	Internal, Clinician
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor,Endocrinology, CMC, Vellore	Internal, Clinician
Dr. SnehaVarkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician
Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. AjithSivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Shyam Kumar NK	MBBS, DMRD, DNB, FRCR, FRANZCR	Professor, Radiology, CMC, Vellore	Internal, Clinician
Dr. Asha Solomon	MSc Nursing	Associate Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

We approve the above amendment as presented.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board.

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

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